

**Europäisches Patentamt** European Patent Office



EP 1 136 071 A2 (13)

## EUROPEAN PATENT APPLICATION (12)

(51) int Ct.?: A61K 31/00, A61K 31/404,	A61K 31/4439, A61K 31/496,	A61K 31/422, A61K 31/5377,	A61K 31/427, A61K 31/454,
(43) Date of publication:	26.09.2001 Bulletin 2001/39	(21) Application pumper 01301078 0	(F.) Appropriate the second se

(22) Date of filing: 05.03.2001	A61K 31/407, A61K 4
	A61P 3/10

15/06,

(72) inventor: Treadway, Judith Lee Groton, Connecticut 06340 (US)	(74) Representative: Hayles, James Richard Pfizer Limited,
(84) Designated Contracting States: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR	Designated Extension States: AL LT LV MK RO SI

	Prizer Limited,
(30) Priority: 22.03.2000 US 191381 P	Patents Department, Ramsgate Road
(71) Applicant: Pfizer Products Inc. Greton, CT 06340-5148 (US)	Sandwich Kent CT13 9NJ (GB)

### Use of glycogen phosphorylase Inhibitors (54)

(57) Individuals in whom Type 2 diabetes melittus has not yet presented, but in whom there is an increased risk of developing such condition, can be treated pro-

phylactically with a glycogen phosphorylase inhibitor; a glycogen phosphorylase a non-glycogen phosphorylase inhibiting and-diselate agent; or a glycogen phosphorylase inhibiting and-diselate agent; or a glycogen phosphorylase inhibitor and an anti-obesity agent.

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#### Description

### Field of the invention

[0001] The invention relates to methods of utilizing glycogen phosphorylase inhibitors in the prophylactic treatment of individuals who have not yet presented with Type 2 diabetes melittus, but in whom there is an increased risk of Background of the invention developing such condition.

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[0002] The diabetic disease state is characterized by an impaired glucose metabolism that manifosts hself in, *inter* sife, elevated blood glucose levels in patients suffering therefrom. Generally, diabetes is classified into two distinct

- (1) Typo 1 diabetes, or insulin-demanding diabotes meilitus (IDDM), which arises when patients lack β-cells producing insulin in their pencreatic glands, and (2) Typo 2 diabetes, or non-insulin dependent diabetes meilitus (NIDDM), which occurs in patients with, *inter alla*,
  - impaired β-ceil function.
- treated with hypoglycemic agents, such as sulfanylureas that stimulate β-cell function, with other agents that enhance the lissue sensitivity of the patients towards Insulin, or with Insulin Itself. Although hypoglycemic agents such as sullevels of pationts, thereby leading to an increased risk of acquiring diabotic complications. Also, many pationts gradually tose the ability to respond to treatment with sulfonyfureas and are thus gradually forced into insulin treatment. This [0003] At present, Type 1 diabetic patients are treated with insulin, while the majority of Type 2 diabetic patients are shift of patlents from oral hypoglycemic agent therapy to insulin therapy is usually ascribed to exhaustion of the B-celis fonylureas have been employed widely in the treatment of NIODM, this treatment is, in many instances, not completely satisfactory. In a large number of NIDDM patients, sulfonylureas have proven ineffective in normalizing blood suga 8 23
- due to a defect in one or more of three primary loci the liver, the beta cell (pancreatic islets), and/or paripheral insulin-responsive tissues (muscle and fat). There is great scientific debate about the primary importance in one loci over that the primary defect could occur in liver, causing elevated hepatic glucose production, which in turn stimulates hyporinsulinemia by the bata-cell and paripheral insulin resistance (Am. J. Physiol., 264 (27), E18-E23, 1983). [0005] This progression could then account for a primary defect in hepatic glucose production to produce secondary [0004] Type 2 diabetes is a heterogeneous disorder which appears to be polygenic in nature. The primary defect that leads to the clinically diagnosed state of Type 2 diabetes is not clearly identifled at this time. It is suspected to be others in the etiology and progression of the disease from the non-diseased state, and at least one reference suggests 8 33
- pancricatic and systemic dystunction, or coupled with existing subthreshold deflects at any of the three loci, to lead from a non-diseased state, to a state of Insulin resistance, and/or impaired glucese tolerance without full presentation of control and insulin sensitivity, and hence prevent or slow the onset or progression to a clinically diagnosed Typo 2 diabetic state, would be useful. Therefore, it is stated also here that glycogon phosphorylase inhibitors would be useful for reducing hopstic glucose production and/or insulin resistance in patients in whom impaired glucose telerance or Type 2 diabetes has not presented but for whom are at increased risk of developing this disease, and/or preventing prediabatic state, including, but not limited to, polycyctic ovary syndrome, pregnancy, growth hormone disorders, an individuals "at risk" for the onset or progression of phenotype to the state of Type 2 diabetes, before reaching the state lype 2 diabetes. This is called an Insulin-resistant state, a Syndrome X state, or a metabolic syndrome state, or e that clinical presentation of Type 2 diabetes could result. For this reason, it is hypothesized here that treatment o at which Type 2 diabetes clinically presents, with a glycogen phosphorylase inhibitor to reduce hepatic glucose pro drogen disorders, and the like. Any of the above conditions could progress to worsen glycemic control to the exten duction and elicit the plethora of effects (both liver and otherwise) to provide efficacy and hence maintain glyce \$ \$ 8
- creased, in some cases resulting in a doubling of glucose output following overnight fasting. Moreover, in these patients, there axists a terring correlation between the increased fasting pleans allucose levels and the rate of hepatic glucose protect and the rate of hepatic glucose protection. See, for examples, therm whateh Fes. 25 and 18-21 (1992). Similarly, hepatic glucose production will be increased in Typo 1 diabetes if the disease is not proporty. duction of glucose is derived either from the release of glucose from stored glycogen or from gluconeogenesis, a de 5-phosphatase. In Type 2 diabetics, however, the regulation of hepatic glucose output is poorty controlled and/or In-In both normal and diabetic individuals, the liver produces glucose in order to avoid hypoglycemia. This pro novo intracellular synthesis of glucose from a gluconeogenesis precursor, a process mediated by the enzyme glucose the disease in patients (people) "at risk" for Type 2 diabetes.

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Printed by Jauve, 75001 PARIS (FR)

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Publication Nos. WO 96/39384 and WO 96/39385. The disclosures of the foregoing are all incorporated herein by reference. As such, gycogen phosphorylase Inhibitors are known to be useful in the treatment of NIDOM by docreasing hepatic glucose production and lowering hypoglycemia. See T.L. Blundell, et al.; Diabetologia, 35, Suppl. 2, 569-576 [0007] Since many axisting forms of diabetes therapy have proven ineffective in echieving completely satisfactory glycemic control, there continues to be a great demand for novel therapoutic approaches. As the diabetic liver is known to have an abnormally augmented rate of glucose production, compounds targeting this abnormal activity are highly in, inter alia, International Application Publication WO 97/31901, and In commonly-assigned International Application desirable. Recently, agents functioning as inhibitors of the hapatic enzyme glucose-6-phosphatase have been disclosed

(1982) and Martin, et al.; Blochemistry, 30, 10101 (1991).
[0008] Regarding the use of anti-diabetic agents for the prophylactic treatment of certain at-stsk individuals, U.S. Pat. No. 5,874,454 discloses the use of certain thiazolidinedione derivatives in treating populations at risk for developing.

NIDDM and complications arising therefrom.

[0009] The methods of instant invention are directed to the use of glycogen phosphorylase inhibitors in treating prophylactically individuals in whom Type 2 diabetes mellitus has not yet presented, but in whom there is an increased risk of developing such condition

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[0010] The invention provides methods of treating prophylactically an individual in whom Type 2 diabetes mellitus has not yet presented, but in whom there is an increased risk of developing such condition, which methods comprise administentage to a Individual in need therefor an effective amount of a glycogen phosphorylase inhibitor. [0011] The glycogen phosphorylase inhibitor, as amployed according to the methods of the invention, preferably comprises a compound selected from the group consisting of:

(i) a compound of formula (i)

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the stereoisomers and prodrugs thereof, and the pharmaceutically acceptable sells of the compounds, stereoisomers, and prodrugs, wherein A, R1, R2, R3, R4, R3, R6, R7, R10, and R11, within the centext of formula (I), are as defined hereinbelow;

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(ii) a compound of formula (ii)

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the stereotsomers and prodrugs thereof, and the pharmaceutically acceptable salts of the compounds, stereoisomers, and prodrugs, wherein A, R1, R2, R3, R4, R5, R9, R7, R10, and R11, within the context of formula (il), are as defined hereinbelow;

(iii) a compound of formula (III)

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the stereolsomers and prodrugs thereof, and the pharmaceutically acceptable salts of the compounds, stereof-somers, and prodrugs wherein R1, R2, and R3, within the context of formula (III), are as defined hereinbelow; and

(iv) a compound of formula (IV)

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the stereolsomers and prodrugs thereof, and the pharmaceutically acceptable sells of the compounds, storeol-somers, and prodrugs, wherein Q, X, Y, Z, Pº, R¹, R², and R³ and R⁴, within the context of formula (IV), are as defined hereinbelow.

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[0012] The invention further provides mothods of treating prophylactically an individual in whom Type 2 diabetes

comprise administering to an individual in need thereot effective amounts of a glycogen phosphorylase inhibitor and a non-glycogen phosphorylase inhibiting and-dlabotic agent, or a glycogen phosphorylase inhibitor and an anti-obosity melitus has not yet presented, but in whom there is an increased risk of developing such condition, which methods agent, preferably in the form of a pharmaceutical composition.

## Detailed Description of the invention

- [0013] The present Invention provides methods of treating prophylactically an individual in whom Type 2 diabetes mellitus has not yet presented, but in whom there is an increased risk of developing such condition, which methods
- [0014] The invention further provides methods of treating prophylactically an individual in whom 1ype z arawwa melitus has not yet presented, but in whom there is an increased risk of developing such condition, which melitude has not yet presented, but in whom there is an increased risk of developing and the province and the pr comprise administering to an individual in need thereof effective amounts of a glycogen phosphorylase inhibitor and comprise administering to an individual in need thereol an effective amount of a glycogen phosphorylase inhibitor [0014] The invention further provides methods of treating prophylactically an individual in whom Type 2 diabetes a non-glycogen phosphorylase inhibiting anti-diabetic agent, or a glycogen phosphorylase inhibitor and an anti-obesity
- agent, preferably in the form of a pharmacourtical composition.

  (1015) Any individual representing a population having an increased risk of presenting with Type 2 diabetes mellitus for 1015 Any individual representing a population having an increased risk of presenting with Type 2 diabetes mellitus may be prophylaticially treated according to the methods of the instant invention. Accordingly, the methods of the invantion are useful for preventing the transition to Type 2 diabetes mellitus of anydisease state or condition associated with risk factors having the potential to cause or induce such transition. Examples of such risk factors may Include, but are not limited to:

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- (ii) risk factors based on an environmental or genetic Type 2 diabetes pre-disposing disease state or condition such as a family history of diabetes, especially in parents or siblings; (i) risk factors associated with classification as an individual having insulin resistance and/or hyperinsulinemia;
- (iii) risk factors predicated on race and/or ethnicity, especially individual membership in a population comprising

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- African-Americana, Hispanica, Native Americana, Asiana, Pacific Islandera, and the like; (iv) risk factors based on genetic mutations affecting β-cell function including defects on chromosome 12, gene HNF-1α (MODY3); defects on chromosome 7, gene glucokinase (MODY2); defects on chromosome 20, gene
  - iton, or otherwise having a genetic mutation or mutations in the insulin raceptor, IRS proteins, glucose transporters, PC-1, glucokinase, UCP-1, ß3 advenergic receptor gene, and the like; (v) risk factors based on genetic defects in insulin action including genetic mutations leading to Type A insulin resistance, acanthosis nigricans, leprechaunism, Rabson-Mendenhall syndrome, lipoatrophic diabetes or condi-HNF-4α (MODY1); defects in mitochondrial DNA, and the like;
- (vi) risk factors based on presence of excess adipose tissue or clinically diagnosed obesity (i.e. ≥ 20% excess of
- normal body weight, or BMI ≥ 27 kg/rr2), especially central obeslty; (vii) risk factors identified through clinical chemistries or diagnostic testing signifying a pre-diabetic state including impaired glucose tolerance (currently defined as impaired glucose response ≥ hours following oral glucose load, 1e. ≥ 140 mg/dl, but <200 mg/dl, with normal glucose fasting value), impaired fasting glucose (currently defined as fasting plasma glucose (FPG) ≥ 110 mg/dl, but < 126 mg/dl), or otherwiso described as having hyperglycomia
- (viii) risk lactors related to physkologic and endocrine changes associated with growth, development, or aging such as classification as a menopausal, pubescent, or aged individual, especially an individual 2 45 years of age:
- experiencing prolonged fasting or starvation, or risk factors associated with eating disorders, including having (k) risk factors related to diet or eating behaviors, including consumption of high fat or high carbohydrate diets, anorexia nervosa or butemia, and the like;
  - sure ≥ 140/90 mmHg in adults, HDL cholesterol levels ≤ 35 mg/dl and/or TG levels ≥ 250 mg/dl, or classification (x) risk factors based on abnormal cardiovascular or blood lipid parameters, such as hypertension, i.e. blood pres
- (xi) risk factors based on reproductive status, such as pregnancy, or a history of gestational diabetes or macrosomia, i.e. the delivery of offspring having a birthweight of >9 lbs.; as having metabolic syndrome, i.e. Syndrome X;
  - (xii) risk factors attributable to muscle wasting due to aging, starvation, exposure to anti-gravity environments

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- paratysis resulting from spinal cord injury, and the like; (xiii) risk factors associated with polycystic ovary syndrome;

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(xiv) risk factors due to organ disease or dysfunction including liver cirrhosis, or renal disease; (xv) risk factors due to conditions resulting in metabolic disturbances; (xvi) risk factors due to endocrine disorders or endocrinopathiles, such as hyperandrogenism, thyrotoxicosis, hyperthyrokdism, insulinoma, glucagonoma, somatostatinoma, aidosteroma, Cushing's Syndrome, pheochromocytoma, acromegaly, hypercortisolemia, and the like;

(xvii) risk factors due to pathophysiologic states Including infection (especially congenital rubella, cytomegalovirus, and the like), toxemia, uremia, sepsis, or trauma;

(xviii) risk factors due to immune-mediated disease such as "stiff man" syndrome, production of anti-insulin receptor antibodies, and the like;

- (xix) risk factors due to drug or chemical exposure, including being treated with insulin-resistance-inducing or hypergypcemia-Inducing agents including, for example, glucoconticoids, cytokines, cylnterferon, thyroid hormone, targeted antipsychotics or antidepressants, vacor, diazoxide, dilantin, HIV protease inhibitors, and the like; (xx) risk factors associated with having a genetic syndrome associated with diabetes including Down's Syndrome, TNFa, thiazides, estrogen-containing products, β-blockers, nicotinic acld, olanzapine and other serotonin receptor-
  - Klinefelter's Syndrome, Wolfram's Syndrome, Freldreich's Syndrome, Huntington's chores, Laurence-Moon-Bledt (xxi) risk factors associated with the long-term detrimental effects caused by the administration of prolonged, el-Syndrome, myotonic dystrophy, porphyrla, Prader-Willi Syndrome, Alzhelmer's Disease, and the like; and evated doses of insulin and/or the presence of ketoacldosis.

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[0016] Aithough any glycogen phosphorylase inhibitor may be employed in accordance with the methods of the instant invention, it is generally preferred that the inhibitor comprise a compound selected from the group consisting of: 5

(i) a compound of formula (i)

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the stereolsomers and prodrugs thereof, and the pharmaceutically acceptable satts of the compounds, stereol-somers, and prodrugs, wherein

the dotted line (---) is an optional bond;

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A is C(H)=, C((C<sub>1</sub>-C<sub>4</sub>)alkyl)= or -C(halo)= when the dotted line (·) is a bond, or A is methylene or -CH( (C<sub>1</sub>-C<sub>4</sub>)alkyl)- when the dotted line (·) is not a bond; R<sub>1</sub>, R<sub>10</sub> or R<sub>11</sub> are each independently H, halo, 4., 6. or 7-nitro, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, fluor-

amethyl, difluoromethyi or trifluoromethyl;

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is H or (C<sub>1</sub>-C<sub>5</sub>)alkyl;

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R<sub>a</sub>ie H, methyl, ethyl, n-propyl, hydroxy(C<sub>1-Ca</sub>)alkyl, (C<sub>1</sub>-C<sub>a</sub>)alkoxy(C<sub>1</sub>-C<sub>a</sub>)alkyl, phenyl(C<sub>1</sub>-C<sub>a</sub>)alkyl, phenyl(C<sub>1</sub>-C<sub>a</sub>)alkyl, phenyl(C<sub>1</sub>-C<sub>a</sub>)alkoxy(C<sub>1</sub>-C<sub>a</sub>)alkyl, thien-2- or -3-yl(C<sub>1</sub>-C<sub>a</sub>)alkyl, or fur-2- or -3-yl (C<sub>1</sub>-C<sub>a</sub>)alkyl wherein said R<sub>4</sub> rings are mono-, di- or tri-substituted independently on carbon with H, halo,

alkyi, isoazo13., 4- or 5-yi(C<sub>1</sub>-C<sub>2</sub>Jaikyi, isothiazo13., 4- or 5-yi(C<sub>1</sub>-C<sub>2</sub>Jaikyi, pyridazh-3- or 4-yi-(C<sub>1</sub>-C<sub>2</sub>Jaikyi, pyrimidu-2., 4-, 5- or 4-yi(C<sub>1</sub>-C<sub>2</sub>Jaikyi, pyrizah-2- or 5-yi(C<sub>1</sub>-C<sub>2</sub>Jaikyi or 1,2-fatratan-2-yi(C<sub>1</sub>-C<sub>2</sub>Jaikyi, whenchen isati preceding P<sub>1</sub> heterocycles are optionally mono- or disubstituted independently with halo, influoromathyi, (C<sub>1</sub>-C<sub>2</sub>Jaikyi, (C<sub>1</sub>-C<sub>2</sub>Jaikoxy, amino or hydroxy and said mono-or di-substituonis are (C,-C₄)alky, (C,-C₄)alkoxy, trifluoromethyl, hydroxy, amino or cyano; or R₄ is pyrid-2·, -3- or -4-yl(C,-C₄)alkyl, thiazol-2·, -4- or -5-yl(C<sub>1</sub>-C<sub>4</sub>)alkyl, imidazol -1·,-2·, -4- or -5-yl(C<sub>1</sub>-C\_Jalkyl, pyrrol-2- or -3-yl(C,-C,)alkyl, oxazol-2-, -4- or - 5-yl-(C,-C,)alkyl, pyrazol-3-, -4- or -5-yl(C,-C,)

R. is H. hydroxy, fluoro. (G.-C.,Jalky). (C.-C.,Jalky). (G.-C.,Jalkanoy). arrino(G.-C.,Jalkoxy, mono-N- or delt-N-(G.-C.,Jalkya). (G.-C.,Jalkya). delt-N-(G.-C.,Jalkya). delt-N-(G.-C.,Jalkya). delt-N-(G.-C.,Jalkoxy). delt-N phonyi, thiazołyi, imidazołyi, 1H-indolyi, Iuryi, pyrrolyi, oxazołyi, isozazołyi, isotniazołyi, pyridazi-nyi, pyrimidinyi, pyrazinyi or 1,3,5-triazinyi and whereln sald procoding P<sub>3</sub> rings are optionally mono-aubstituted with halo, (C<sub>1</sub>-C<sub>4</sub>)alky), (C<sub>1</sub>-C<sub>4</sub>)alkoxy, hydroxy, amino or trifluoromethyl and said mono-substitu

ents are bonded to carbon;

R<sub>7</sub> Is H, fluoro or (C<sub>1</sub>-C<sub>5</sub>)alkyl; or R<sub>5</sub> and R<sub>7</sub> can be taken together to be oxo;

Re is carboxy, (C1-Ca)alkoxycarbonyl, C(O)NRBRs or C(O)R12,

R<sub>8</sub> is H, (C<sub>1</sub>-C<sub>2</sub>)alkyl, hydroxy or (C<sub>1</sub>-C<sub>2</sub>)alkoxy, and R<sub>9</sub> Is H, (C<sub>1</sub>-C<sub>2</sub>)alkyl, hydroxy, (C<sub>1</sub>-C<sub>8</sub>)alkoxy, methylene-perlluoinated(C<sub>1</sub>-C<sub>8</sub>)alkyl, phenyl, pyrdyl, thienyl, furyl, pyrrobyl, pyrrolidinyl, oxazobyl, thiazolyl, inidazolyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, sokazolyi, isothiazolyi, pyranyi, piperidinyi, morpholinyi, pyridazinyi, pyrimidinyi, pyrazinyi, piperazinyi or

1,3,5-triazinyi wherein sald preceding P<sub>e</sub> rings are carbon-nitrogen linked; or P<sub>e</sub> is mono-, di- or tri-substituted (C<sub>1</sub>-C<sub>2</sub>)alkyi, wherein sald substituents are independently H, hydroxy,

isothiazolyi, pyranyi, pyridinyi, piperidinyi, morpholinyi, pyridazinyi, pyrimidinyi, pyrazinyi, piperazinyi or R<sub>9</sub> is mono- or di-substituted (C<sub>1</sub>-C<sub>5</sub>)alkyl, wherein said substituents are independently phenyl, pyridyl furyl, pyrrolyl, pyrrolidinyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, isoxazolyl amino, mono-N- or dl-N,N-(C1-C5)alkylamino; or

wherein the nonaromatic nitrogen-containing R<sub>g</sub> rings are optionally mono-substituted on nitrogen with (C<sub>1</sub>-C<sub>6</sub>)alkyl, benzyl, benzoyl or (C<sub>1</sub>-C<sub>6</sub>)alkoxycarbonyl and wherein the R<sub>9</sub> rings are optionally mono-substituted on carbon with halo, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, hydroxy, amino, or mono-N- and di-N,N (C<sub>1</sub>-1,3,5-triazinyl

lldin-3-yl, 2-, 4-, and/or 5- mono- or dl- substituted thlazolldin-3-yi, 2-, 4-, and/or 5- mono- or dl- substituted or disubstituted pyrrolldin-1-yl, 3-, 4- and/or 5-, mono-, di- or tri-substituted pipendin-1-yl, 3-, 4-, and/or 5-mono-, di-, or tri-substituted piperazin-1-yl, 3-substituted azetidin-1-yl, 4- and/or 5-, mono- or di-substituted , 2-oxazinan-2-yl, 3-and/or 4-mono- or di-substituted pyrazolidin-1-yl, 4- and/or 5-, mono- or di-substituted isoxazolidin-2-yi, 4- and/or 5-, mono- and/or di-substituted isothiazolidin-2-yi wherein said R<sub>12</sub> substituents are independently H, halo, (C,-C<sub>3</sub>)-alkyl, hydroxy, amino, mono-N- or di-N,N-(C,-C<sub>3</sub>)alkylamino, (ormy, oxo, hydroxylmino, (C<sub>1</sub>-C<sub>3</sub>)alkykarbamoyl, (C<sub>1</sub>-C<sub>S</sub>)alkylamino provided that no quaternized nitrogen is included and there are no nitrogen-oxygen, nitro R<sub>12</sub> is piperazin-1-yt, 4-(C<sub>1</sub>-C<sub>4</sub>)alkyhiperazin-1-yt, 4-formyhiperazin-1-yt, morpholino, thiomorpholino 1-oxothlomorpholino, 1,1-dioxo-thlomorpholino, thlazolidin-3-yl, 1-oxo-thlazolidin-3-yl, 1,1-dioxo-thlazoli R<sub>12</sub> is 3- and/or 4-mono-or di-substituted oxazetidin-2-yl, 2-, 4-, and/or 5- mono- or di-substituted oxazo ا-oxothiazolidin-3-y1, 2-, 4-, and/or 5- mono- or di- substituted 1,1-dioxothiazolidin-3-y1, 3- and/or 4-, mono din-3-yi, 2-(C<sub>1</sub>-C<sub>6</sub>)alkoxycarbonylpyrrolidin-1-yi, oxazolidin-3-yi or 2(R)-hydroxymethylpyrrolidin-1-yi; or gennitrogen or nitrogen-halo bonds;

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(II) a compound of formula (II)

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C,Jalkoxyimino, (G₁-C₄)alkoxymethoxy, (G₁-C<sub>6</sub>)alkoxycarbonyi, carboxy(G₁-C₅)alkyl or hydroxy(G₁-C₅) alkyl;

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the stereoisomers and prodrugs thereof, and the pharmaceutically acceptable salts of the compounds, stereoisomers, and prodrugs,

wherein

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the dotted line (---) is an optional bond;

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A is -C(H)=, -C((C<sub>1</sub>-C<sub>2</sub>)alkyt)=, -C(halo)= or -N=, when the dotted line (-) is a bond, or A is methylene or -CH((C<sub>1</sub>-C<sub>2</sub>)alkyt)-, when the dotted line (-) is not a bond; R1, R1<sub>0</sub> or R1, are sech independently H, halo, cyano, 4 ·, 6 ·, or 7 ·ntro, (C<sub>1</sub>-C<sub>2</sub>)alkyt, (C<sub>1</sub>-C<sub>2</sub>)alkoxy, fluor-

omethyl, difluoromethyl or trifluoromethyl;

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R<sub>3</sub> is H or (C<sub>1</sub>-C<sub>5</sub>)alkyt;

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R<sub>2</sub> is H. methyt, ethyl. n-propyl, hydroxy(C<sub>1</sub>-C<sub>2</sub>)alkyl, (C<sub>1</sub>-C<sub>2</sub>)alkoxy(C<sub>1</sub>-C<sub>2</sub>)alkyl, phonyl(C<sub>1</sub>-C<sub>2</sub>)alkyl, thorhydroxy(C<sub>1</sub>-C<sub>2</sub>)alkyl, thorhydroxy(C<sub>1</sub>-C<sub>2</sub>)alkyl, thorhydroxy(C<sub>1</sub>-C<sub>2</sub>)alkyl, thorhydroxy(C<sub>1</sub>-C<sub>2</sub>)alkyl, thorhydroxy corbyd (C<sub>1</sub>-C<sub>2</sub>)alkyl, thorhydroxy corbyd (C<sub>1</sub>-C<sub>2</sub>)alkyl, thorhydroxy amino, cyano or 4.5-dlhydro-1.H-midazol-2.Y; or 4.5 pride<sup>2</sup>, so 7 e-yi(C<sub>1</sub>-C<sub>2</sub>)alkyl, thacol-2.4 or 4.5 pride<sup>2</sup>, e. 4 or 4.5 yi(C<sub>1</sub>-C<sub>2</sub>)alkyl, thacol-2.4 or 4.5 yi(C<sub>1</sub>-C<sub>2</sub>)alkyl, thacol-2.4 or 4.5 yi(C<sub>1</sub>-C<sub>2</sub>)alkyl, prizacl-3.4 or 4 stituents are bonded to carbon; or

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R<sub>4</sub> is R<sub>15</sub>-carbonyloxymethyl, wherein said R<sub>15</sub> is phenyl, thiazolyl, irnidazolyl, 1H-indolyl, furyl, pyrrolyl, oxazolyi, pyrazolyi, isoxazolyi, isothiazolyi, pyridyi, pyridazlnyi, pyrimidinyi, pyrazinyi or 1,3,5-triazinyi and wherein said preceding A<sub>15</sub> rings are optionally mono- or di-substituted independently with halo, amino, hydroxy, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy or trifluoromethyl and sald mono- or di-substituents are bonded to

Re is carboxy, (C<sub>1</sub>-C<sub>8</sub>)alkoxycarbonyl, benzyłoxycarbonyl, C(O)NR<sub>8</sub>R<sub>9</sub> or C(O)R<sub>12</sub> is H, methyl, ethyl, n-propyl, hydroxymethyl or hydroxyethy

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is H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, cyclo(C<sub>3</sub>-C<sub>6</sub>)alkyl, cyclo(C<sub>3</sub>-C<sub>6</sub>)alkyl(C<sub>1</sub>-C<sub>5</sub>)alkyl, hydroxy or (C<sub>1</sub>-C<sub>6</sub>)alkoxy; and

R<sub>9</sub> is H, cyclo(C<sub>3</sub>-C<sub>8</sub>)alkyl, cyclo(C<sub>3</sub>-C<sub>8</sub>)alkyl(C<sub>1</sub>-C<sub>8</sub>)alkyl, cyclo(C<sub>4</sub>-C<sub>7</sub>)alkonyl, cyclo(C<sub>3</sub>-C<sub>7</sub>)alkyl(C<sub>1</sub>-C<sub>5</sub>) alkoxy, cyclo(C<sub>3</sub>-C<sub>7</sub>)alkyloxy, hydroxy, methylene-perfluorinated(C<sub>1</sub>-C<sub>8</sub>)alkyl, phenyl, or a heterocycle whorein said heterocycle is pyridyl, furyl, pyrrolyl, pyrrolidinyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyrazolinyi, pyrazolidinyi, isoxazolyi, isothiazolyi, pyranyi, pyridinyi, piporidinyi, morpholinyi, pyridazinyi, pyrimldinyi, pyrazinyi, plperazinyi, 1,3,5-trlazinyi, benzothiazolyi, benzoxazolyi, benzimidazolyi, thiochromanyl or tetrahydrobanzothiazolyl wherein said heterocycle rings are carbon-nitrogen linked, or

R<sub>9</sub> is (C<sub>1</sub>-C<sub>8</sub>)alkyl or (C<sub>1</sub>-C<sub>8</sub>)alkoxy wherein said (C<sub>1</sub>-C<sub>8</sub>)alkyl or (C<sub>1</sub>-C<sub>8</sub>)alkoxy is optionally monosubsti-tuted with cyclo(C<sub>4</sub>-C<sub>7</sub>)alken-1-yl, phenyl, thienyl, pyridyl, turyl, pyrrolyl, pyrrolidinyl, oxazolyl, thiazobyl, imidazolyl, pyrazolyl, pyrazolinyl, pyrazolidnyl, isoxazolyl, isothiazolyl, pyranyl, piperidinyl, morphollinyl, thiomorpholinyl, 1-oxothiomorpholinyl, 1,1-dioxothiomorpholinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piper azinyi, 1,3,5-trfazinyi or indolyl and wherein sald (C<sub>1</sub>-C<sub>8</sub>)alkyi or (C<sub>1</sub>-C<sub>8</sub>)alkoxy are optionally additionally

independently mono- or di-substituted with halo, hydroxy, (C,-C<sub>5</sub>)alkoxy, amino, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>4</sub>)alkylamino, cyano, carboxy, or (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl; and

alkylamino(C<sub>1</sub>-C<sub>2</sub>)alkyl, (C<sub>1</sub>-C<sub>2</sub>)alkoxy(C<sub>1</sub>-C<sub>2</sub>)alky, amino, mono-N· or di-N.N-(C<sub>1</sub>-C<sub>2</sub>)alkylamino, cyano, carboxy, (C<sub>1</sub>-C<sub>2</sub>)alkoxycarbonyl, carbamoyl, formyl or trifluoromethyl and said R<sub>3</sub> rings may optionally be wherein the R<sub>e</sub> ings are optionally mono- or di-substituted independently on carbon with hato, (C<sub>1</sub>-C<sub>4</sub>) alky, (C<sub>1</sub>-C<sub>4</sub>)alky, (C<sub>1</sub>-C<sub>4</sub>)alky, (C<sub>1</sub>-C<sub>4</sub>)alky, (C<sub>1</sub>-C<sub>4</sub>)alky, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>4</sub>) additionally mono- or di-substituted independently with (C,-Cs)alkyl or halo;

dro-benzo[1,4]oxazin-4-yt, 2,9-dihydro-benzo[1,4]-thiazina-4-yt, 3,4-dihydro-2H-quinoxalin-1-yt, 3,4-dihy-dro-benzo[c][1,2]oxazin-1-yt, 1,4-dihydrobenzo[c][1,2]oxazin-3-yt, 3,4-dihydro-benzo[o][1,2]-oxazin-2-yt, 3H-benzo[d][3coxazol-1-yt or ezepen-1-yt, R<sub>12</sub> is morpholino, thiomorpholino, 1-oxothiomorpholino, 1,1-dioxothiomorpholino, thiazolidin-3-yi, 1-ox-othiazolidin-3-yi, 1,1-dioxothiazolidin-3-yi, pyrrolidin-1-yi, piperidin-1-yi, piperiazin-1-yi, piperiazin-4-yi, azetidin-1-yi, 1,2-oxazinan-2-yi, pyrazolidin-1-yi, isoxazolidin-2-yi, isothiazolidin-2-yi, 1,2-oxazetidin-2-yi, oxazolidin-3-y1,3,4-dihydrolsoquinolin-2-y1,1,3-dihydrolsoindol-2-y1,3,4-dihydro-2H-quinol-1-y1,2,3-dihy-

bonyi, (G,-C<sub>3</sub>)alkoxycarbonyi(G<sub>+</sub>C<sub>3</sub>)alkyi, (G<sub>+</sub>C<sub>4</sub>)alkoxycarbonylamino, carboxy(G<sub>+</sub>-C<sub>3</sub>)alkyi, carbamoyi (G<sub>+</sub>C<sub>5</sub>)alkyi, mono-N- or di-N,N-(G<sub>+</sub>-C<sub>5</sub>)alkyicarbamoyi(G<sub>+</sub>-C<sub>3</sub>)alkyi, hydroxy(G<sub>+</sub>-C<sub>5</sub>)alkyi, (G<sub>+</sub>-C<sub>4</sub>)alkoxy wherein said R<sub>12</sub> rings are optionally mono-, di- or tri-substituted independently with halo, (C<sub>1</sub>-C<sub>3</sub>)alkyl, (C<sub>1</sub>-C<sub>3</sub>)alkoxy, hydroxy, amino, mono-N· or di-N<sub>1</sub>N·(C<sub>1</sub>-C<sub>3</sub>)alkylamino, formyl, carboxy, carbamoyl, mono-N· or di-N·N·(C<sub>1</sub>-C<sub>2</sub>)alkylcarbamoyl, (C<sub>1</sub>-C<sub>8</sub>)alkoxy(C<sub>1</sub>-C<sub>2</sub>)alkoxy, (C<sub>1</sub>-C<sub>2</sub>)alkoxycarbonyl, benzyloxycar-(C,-C,)alixy, amino(C,-C,)alixy, mono-N- or di-N,N-(C,-C,)alixylamino(C,-C,)alixy, oxo, hydroxyimino or (C₁-C₅)atkoxyimino and wherein no more than two substituents are selected from oxo, hydroxyimino or (C<sub>1</sub>-C<sub>6</sub>)alkoxyimino and oxo, hydroxyimino or (C<sub>1</sub>-C<sub>6</sub>)alkoxyimino are on nonaromatic carbon; and

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wherein said  $R_{12}$  rings are optionally additionally mono- or di-substituted independently with  $(C_1 - C_3)$ alkyl

(iii) a compound of formula (III)

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the stereoisomers and prodrugs thereof, and the pharmaceutically acceptable salts of the compounds, stereoisomers, and prodrugs, wherein

R<sup>1</sup> is (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)cycloalkyl, phenyl or phenyl independently substituted with up to three (C<sub>1</sub>-C<sub>4</sub>)alkyl,

C1-C4)alkoxy or halogen;

 $\mathbb{R}^2$  is  $(\mathbb{C}_+,\mathbb{C}_+)$ alkyl optionally substituted with up to three fluoro atoms; and  $\mathbb{R}^3$  is  $(\mathbb{C}_+,\mathbb{C}_+)$ alkyl, halo or trifluoromethyl; phenyl substituted at the para position with  $(\mathbb{C}_+,\mathbb{C}_+)$ alkyl, halo or trifluoromethyl; phenyl substituted at the ortho position with fluoro; or phenyl substituted at the ortho position with fluoro; and

(N) a compound of formuta (IV)

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the stereolsomers and prodrugs thereof, and the pharmaceutically acceptable salts of the compounds, stereol-

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somers, and prodrugs, wherein

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each - - - - Is Independently a bond or is absent, provided that both - - - - are not simultaneously bonds; Q is anyi, substitued anyi, heteroanyi, or substitued heteroanyi each Z and X are independently (C, CH or CH<sub>2</sub>), N, O or S; X¹ is NRe, -CH<sub>2</sub>·, O or S;

R¹ is hydrogen, halogen, -OC₁-Cealkyl, -SC₁-Cealkyl, -C-Cealkyl, -C-Cealkyl, -C-Cealkyl, -C-Cealkyl, -N-C-Cealkyl, -N-C-Cealkyl, -N-C-Cealkyl, -N-C-Cealkyl) - -CO-Cealkyl, -C-Cealkenyl, or -C-Cealkylyli, esech R\* and R\* is independently hydrogen or -C₁-Cealkyl; Y is

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R\* is -C(=0)-A;

A Is -NR4H4, -NR4CH2CH2OR4

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each R<sup>d</sup> is Independently hydrogen, C<sub>1</sub>-C<sub>8</sub>alkyl, C<sub>1</sub>-C<sub>8</sub>alkoxy, aryl, substituted aryl, heteroaryl, or substituted

heteroaryt; each Re is independently hydrogen, -C(=0)OR\*, -CR\*, -SR\*, or -MR\*R\* and each n is independently 1-3.

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[0017] The compounds of formula (i), the stereoisoners and prodrugs thereof, and the pharmsceutically acceptable sails of the compounds, stereoisoners, and prodrugs, may be prepared as described in the aforementioned international Application Publication No. WO 96/39385.

[0018] A particularly preferred subgroup of formula (i) compounds are those compounds selected from the group consisting of:

5,6-dichloro-1H-indole-2-carboxylic acid-{{15}-{(R}-hydroxy-(methoxy-methylcarbamoyr)-methyl]-2-phenyl-ethyl) 5-chlore-1H-indole-2-carboxylic acid-{(1S)-((R)-hydroxy-dimethylcarbamoylmethyl)-2-phenyl-ethyl}-amide;

acid-{(1S)-[(R)-hydroxy-{methoxy-methylcarbamoyl)-methyl]-2-phenyl-ethyl}-5-chloro-1H-Indole-2-carboxylic

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acid-((1S)-((R)-hydroxy-{(2-hydroxy-ethyl)methyl-carbamoyl]-methy}-2-phenyl-5-chloro-1H-indole-2-carboxylic

5-chioro-1H-indole-2-carboxylic acid-((1S)-((R)-hydroxy-[methyl-(2-pyridin-2-yl-ethyl)-carbamoyl]-methyl]-2-phe

5-chloro-1Hindole-2-carboxylic acid-{(1S}-benzyl-(2R}-hydroxy-3-{4-methylpipenzlin-1-yl)-3-oxo-propyl}-amide; 5-chloro-1H-Indole-2-carboxylic acid-{(1S}-benzyl-(2R}-hydroxy-3-{3-hydroxyazetdin-1-yl)-3-oxo-propyl}-amide; 5-chloro-1H-indole-2-carboxylic acid-{(1S}-benzyl-(2R)-hydroxy-3-isoxazolidin-2-yl-3-oxo-propyl)-amide;

5-chloro-1H-indole-2-carboxylic acid-[(1S)-benzyl-(2R)-hydroxy-3-((3S)-hyd roxy-pyrrolidin-1-yl)-3-oxo-propyll-5-chloro-1H-indole-2-carboxylic acid-((1S)-benzyl-(2R)-hydroxy-3-(1,2]oxazlnan-2-yl-3-oxo-propyl)-amide;

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5-chloro-1H-indole-2-carboxyilc acid-[(1S)-benzyl-3-((3S,4S)-dihydroxypyrrolidin-1-yi)-(2R)-hydroxy-3-oxo-pro-

5-chloro-1H-Indola-2-carboxylic acid-{(1S)-benzyl-3-((3R,4S)-dihydroxypyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyl]-amide; and

5-chloro-1H-indole-2-carboxylic ecid-((1S)-benzyl-(2R)-hydroxy-3-morpholin-4-yl-3-oxo-propyl)-amida; the stare-olsomers and prodrugs thereof, and the pharmaceutically acceptable satts of the compounds, stereolsomers, and

salts of the compounds, stereobsomers and prodrugs thereof, and the pharmaceutically acceptable tions of the compounds, stereobsomers, and prodrugs, may be prepared as described in the aforementioned international Application Publication No. WO 96/39364.

[0020] A particularly preferred substruction of formula American American American American 8

consisting of:

5-chloro-1H-indole-2-carboxylic ecid-[(1S)-benzyl-2-(3-hydroxylminopyrrolldin-1-yl)-2-oxo-ethyl]-amide; 8

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5-chloro-1H-Indole-2-carboxylic acid-{2-(cis-3,4-dihydroxy-pyrrolidin-1-yi)-2-oxo-ethyll-amide; 5-chloro-1H-Indole-2-carboxylic acid-{(15)-benzyl-2-(cis-3,4-dihydroxypyrrolidin-1-yi)-2-oxo-ethyll-amide;

5-chloro-1H-indole-2-carboxylic acid-{2-(1,1-dioxo-thiazolidin-3-yl)-2-oxoethyl}-amide;

5-chloro-1H-indole-2-carboxylic acid-(2-oxo-2-thiazolidin-3-yl-ethyl)-amide;

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5-chloro-1H-indole-2-carboxylic acid.{1S}-(4-lluoro-benzyl)-2-(4-hydroxypiperidin-1-yl)-2-oxo-ethyll-amide; 5-chloro-1H-indole-2-carboxylic acid.{1S}-benzyl+2-((3RS)-hydroxy-piperidin-1-yl)-2-oxo-ethyll-amide; 5-chloro-1H-Indole-2-carboxylic acid-2-oxo-2-((1RS)-oxo-1-thlazolidin-3-yl)athylj-amide;

5-chloro-1H-indole-2-carboxylic acid {(1S)-(2-fluoro-benzyl)-2-(4-hydroxypiperidin-1-yl)-2-oxo-ethyl]-amide 5-chloro-1H-indole-2-carboxylic acid-(1S)-benzyl-2-(3-hydroxy-azetidin-1-yl)2-oxo-ethylj-emide

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5-chloro-1H-indole-2-carboxylic acid-(15)-benzyt-2-(3-hydroxylmino-azatidin-1-yl)-2-oxy-athyl)-amide; and 5-chloro-1H-indole-2-carboxylic acid-(15)-benzyt-2-(4-hydroxylmino-pipendin-1-yl)-2-oxo-ethyl)-amide; the ster-soisomers and prodrugs thereof, and the pharmaceutically acceptable salts of the compounds, stereoisomers, and prodrugs.

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[0022] By "halo" is meant chloro, bromo, lodo, or fluoro. [0023] By "alkyt" is meant straight chain or branched saturated hydrocarbon Exemplary of such alkyl gròups (assuming the designated length encompasses the particular example) are methyl, ethyl, propyl, isopropyl, bulyl, sec-[0021] The compounds of formula (III), the stereoisomers and prodrugs thereof, and the pharmaceutically acceptable satis of the compounds, stereoisomers, and prodrugs, may be prepared according to the following synthetic method-ologies. The following definitions are applicable with respect to the compounds of formula (!!!). [0022] [0023]

butyi, *ter*rbutyi, pentyi, isopentyi, hexyi, isohexyi, and so forth. [0024] By "alkoxy" is meant straight chain or branched saturated alkyl bonded through an oxy. Exemplary of such

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alkoxy groups (assuming the designated length encompasses the particular example) are methoxy, ethoxy, propoxy, sopropoxy, butoxy, isobutoxy, tert-butoxy, pentoxy, isopentoxy, hexoxy and isohexoxy.

[0025] The expression "prodrug" refers to compounds that are drug procursors, which, following administration, re-lease the drug *in vin*o via a chemical or physiological process (e.g., a prodrug on being brought to the physiological pH is converted to the desired drug form).

[0026] As used herein, the expressions "reaction-inert solvent" and "inert solvent" refers to a solvent or mixture of solvents which does not interact with starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

[0027] The chemist of ordinary skill will recognize that certain compounds of formula (III) may contain one or more atoms which may be in a particular stereochemical or geometric configuration, giving rise to stereolsomers and con-igurational isomers. All such isomers and mixtures thereol are included in this invention. 5

[0028] In general, the compounds of formula (III) can be made by processes including those known in the chemical ents, particularly in light of the description contained herein. Certain processes for the manufacture of formula (III) compounds are illustrated hereinbelow in the following reaction schemes.

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SCHEME II

[0029] According to Scheme I, the compounds of formula (III), wherein R1, R2 and R3 are as defined hereinabove may be prepared by either of two general procedures which involve outling a carboxylic acid or carboxylic acid ested ested derivative of formula 10. When the coupling it performed is 10 minute 10. When the coupling it performed using a compound of formula 11. When the coupling is performed using a compound of formula 2 the immediate product is a compound of formula (III). When the coupling is performed using a compound of formula 6, which compound contains a protected ketone moley, the intermediat result is the formulation of a compound of formula (III) through result is the formulation of a compound of formula 9 which may then be converted into a compound of formula (III) through

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[0030] Typically, the deprotection of the formula 9 compounds may be effected using methods well known to one of decings skill in the art, for example, the methods described in "Protecting Ghoups" in Organic Synthesia; "Second Edition, TW. Groens and PG.M. Wulley, John Willoy and Sons, Inc., 1991. Generally, the compound of formula 9 is a dissolved in a reaction-hort solvent such as tetrahydrofuran (THF) and strong aqueous acid is added. The temperature of the reaction may be valed from 9°C to 50°C. Generally, however, the reaction performed for one of the starting meterial has reacted as determined by thin layer chorantography or other analytical technique well known to those skilled in the art. Ordinarily, the reaction is stirred for about filteen minutes to adout when y-low hours, and profestably for about one hour. The resulting compound of formula (III) is then isolated according to methods well known to one of ordinary skill in the art.

[0031] The coupling reaction referred to hereinabove is used to generate the compounds of formula (III) directly from the compounds of formula 3, or to generate the compounds of formula 6. The coupling reaction is most readily accomplished by reacting a caboxylic acid seter derivative of formula 6 or formula 8. The coupling appropriate antiline derivative of formula 10, Typically, a compound of formula 6 or formula 10 are section intert selves (4A) are then acidos and the reaction mixture intert selvent and a compound of formula 10 is added. Molecular sleves (4A) are then acidos and the reaction mixture is generally heated at the reflux temperature of the chosen solvent until the starting materials are no longer present is generally heated at the reflux temperature of the chosen solvent until the starting materials are no longer present

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as determined by thin layer chromatography or other analytical techniques that will be well known to one of ordinary skill in the art. The coupled product of formula 9 or formula (III) is then isolated according to methods well known to those skilled in the art.

[0022] Attamatively, the compounds of formula (III) may be prepared according to the procedure set forth in Scheme III. In this procedure, a compound of formula (III) is a set efforth in Scheme III. in the procedure and the activated arride such as a NN-dehenyluride of formula (III). Typicially, the compound of formula (III). Typicially, the compound of formula (III). Typicially, the compound of formula (III). Typicially, the secondary alkyly and R3 are as deezerable henelinable, is lastissived in a subtable solvent and treated with base which is strong enough to deperconate the carbon atom eights to the carbonyl group. The anion thus formed is treated with the activated arride compound and the reaction mature is stirred for about 16 hours to about 7 days. Typicially, the reaction is complete after stirring for about three days. The reaction mixture is then addited to provide the compound of formula (III).

[0033] The compounds of formulae 6 and 7 in Scheme i may be prepared by standard acylation chemistry well known for one of ordinary skill in the at. For example, the compounds of formula 4 are explaided directly, when Rf is tertary alkyl or anyl, by neating the arm For example, the compound of formula 4 unider standard acylation conditions, e.g.: base and exylating agent, to obtain the compound of formula 8. When R is primary or secondary alkyl, the ketone molety attached to the 5-position of the oxindoir infig must be protected using standard ketone protecting groups as set forth in Greene and Wuls, supra. The protected compound of formula 5 is then acylated in the same manner as the compound of formula 4 to obtain the compound of formula 7. The acylation reaction described in this paragraph is readily carired out lesing procedures well known to those skilled in the art of by using methods analogous to those set forth in U.S. Pat. No. 4, 686,224, the teachings of which are incorporated herein by reference. Deprotection, if required, is performed using methods analogous to those set forth in Cheene and Wuts, supra.

[0034] The compounds of formulae 1, 2, 3, 4 and 10 are prepared according to methods well known to those skilled in the art. Further, the starting materials and reagents for the above described reaction schemes are also readily avail- able from commercial sources or can be readily synthesized by those skilled in the art using conventional methods of

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organic synthasis.

10035] The compounds of formula (III) may have an asymmetric carbon atom and therefore are racemic mixtures of enantiomers when prepared from nonoptically active intermediates and reagents. Enantiomers can be separated by reacting the enantiomeric mixture with an appropriate optically active compound (e.g. amine) to form a mixture of district asterocomeric satis of the compound of formula (III) and separating the disstorecomers by crystalization or other method well known to those skilled in the art. If will be recognized by those skilled in the art that recemization of the optically each center may occur upon removal of the ammonium counterion. Therefore, when resolving the compounds of formula (III) using optically active amines such as naturally occurring amine acids protected as carboxylic acid esters or other pharmacounteally acceptable protected amine acids. Other physical resolution (exchiques such as chromatography are well known to those skilled in the att and these techiques may also be used to resolve the enantiomers of formula (III), and classrenomers and enantiomers and mixtures thereof are intended to be included within the scope of the general (III).

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(1035) It will be further recognized that the compounts of formub (III) are acidic and they may form a salt with a paramaceutically acceptable cancin. All such salts are acide and they may form a salt with a py conventional methods well known to one of ordinary sall in the art. Typical bases used to form such cationic salts are a acidium hydroxide, sodium methodde, sodium ethoxide, cadium ethoxide, potables are an experimentally of a sodium hydroxide, protections are sodium hydroxide, protections are sodium hydroxide, protections of the protection of the protection in the cation one salts can be prepared simply by contacting the acidic and basic entities, usually in a stochhomerbre ratio, in either an activeous, non-equeous or partially equeous medium, as deemed appropriate. The salts may then be recovered either by fitzation, by procipitation with a non-solvent followed by filtration, by evaporation of the solvent, or, in the case of aqueous solutions, by hyphilization, as deemed appropriate.

(0037] In addition, when the compounds of general formula (III) form hydrates or solvates they are also intended to be included within the ecope of the invention. 50 (19038) NIAR spectra were recorded on a Varian XI.-300 (Varian Co., Palo Alto, California) or Bruter AM-300 spactromater (Bruker Co., Billance, Massachuseatha) at about 23°C at 300 Mykr for proton and 75.4 mHz for carbon nucleii. Chemical shifts are expressed in patric per million downfield from timethylisine.

[0039] Column chromatography was performed with Amicon silica gel (30 uM, 60A pore size) (Amicon D Vision, W. R. Graze & Co., Baverly, Mass.) in glass columns under low nitrogen pressure. Unless otherwise specified, negants were used as obtained from cormercial sources. Direthylformanide, 2-propanol, letrahydroluran, and dichlorometh-ane were used as reaction solvents were the emhydrous grade supplied by Adirch Chemical Company (Milwaukee, Wisconshi), Microanshyses were performed by Schwartxlopf Microanalylical Laboratory, Woodside, NY. The ferms \*concontrated\*\* and \*coevaporated\*\* felor to removal of solvent at water aspirator pressure on a rotary evaporator with a

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bath temperature of < 45°C.

Example 1

5 - Scatyl-1-ethyl-2-oxo-2,3-dihydro-1H-indole-3-carboxylic acid (3-phenylcarbamoylphenyl)-amide

[0040]

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[D041] Step A. 1-Ethyl-5-(2-methyl-(1.3)dioxolem-2-y)-2-oxo-2.3-dihydro-1H-indole-3-centooxylic seld (3-phenylcarbemoyl-phenyl)-smide. 1-Ehyl-5-(2-methyl-(1.3)dioxolem-2-y)-2-oxo-2.3-dihydro-1H-indole-3-centooylic seld mothyl ester (3.6 g. 11.8 mmol) and 3-emino-N-phenyl-penzamide (5.0 g. 24 mmol) were combined in benzene (160 mL) in a flask filted with a Soxylic toxilahing activated 4A molecular sleves. The mixture was heated to reflux for 30 min, then

cooled, washed with 0.1 N HCl (2 X 30 mL), water and brine, dried over magnesium sulfate and concentrated in vecuo to a dark orange foam which was purified by flash-chromatography (chloroforny methanol, 20:1) to give a slightly

foarny solld (3.75 g, 66%)

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[0042] Stop B. <u>5.Acalyl-1-ethyl-2-oxo-2-3-dihydro-1H-Indole-3-carboxylic acid (3-phenylcarbamoyl-phenyl)-emide.</u>
To a solution of 1-ethyl-5-(Zenathyl-11.3)disoxlan-2-yl-2-oxo-2,3-dihydro-1H-Indole-3-carboxylic acid (3-phanylcar-1-bamoyl-phenyl)-amide (the title compound of Exmple 1, Stop A, 3.75 g, 7.8 mmol) in THF (70 mL) was added 2 with ethyl accidenty) acid and a strong and a troom temperature for 1 hour then poured into water (300 mL) and extracts were washed with water and brine, dried over magnesium sulfate and concentrated in vacuo to laftor an enange foam. The foam was dissolved in a small emnount of ethyl accides and procipitated with hexare to yield at an solid, which was differed on high vacuum (mp 173-175 °C, 2.5 g, 78%), Cabculated for C<sub>2</sub>eH<sub>22</sub>N<sub>3</sub>O<sub>4</sub>; C70.74, H 5.25; N 8 5.2; found C70.91; H 5.56; N 9.25.

Examples 2-15

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[0043] Examples 2 to 15 were prepared from the appropriate starting materials in a manner analogous to the method of Example 1, with variations in reaction time, temperature, and reagents as noted.

Example 2

[0044]

[0045] 5-Acatyl-1-ethyl-2-oxo-2,3-dihydro-1H-indole-3-carboxylic acid (3-cyclohexylcarbemoyl-phenyl)-amide. Prepared as in Example 1 from 1-ethyl-5-(2-methyl-1,3)dioxolan-2-yl)-2-oxo-2,3-dihydro-1H-indole-3-carboxylic acid methyl ester and 3-amino-N-cyclohexyl-benzamide. Purified by trituration in ethyl acetate. mp 180°C dec.

Example 3

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[0046]

NH O H

[0047] S.Aceyk-I-athyt-2-oxo-2-3-dihydro-1H-indole-3-carboxylic acid [3-(4-chlorophenylcarbamoyl)-phenyl]; amide, Prepared as in Example 1 from 1-ethyl-5-(2-methylf; 3|dioxolan-2-yl)-2-oxo-2,3-dihydro-1H-indole-3-carboxylic acid methyl ester and 3-amino-N-(4-chloro-phenyl)-benzamide. Recrystallized from ethyl acetate - hexanes, mp 119-121 °C.

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Example 4

[0048]

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[0049] 5-Acatyl-1-ethyl-2-oxo-2,3-dihydro-1H-indole-3-carboxylic ecid (3-p-tolylcarbamoyphenyl)-emide. Prepared as in Example 1 from 1-ethyl-5-(2-methyl-1,3)dioxolan-2-yl)-2-oxo-2,3-dihydro-1H-indole-3-carboxylic acid methyl ester and 3-amino-N-(p-tolyl)-benzamide. Purified by trituration in ethyl acetate / hexanes.mp 168 dec.

Example 5

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[0020]

[0051] 5-Acetyl-1-ethyl-2-oxo-2,3-dihydro-1H-indole-3-carboxylic acid [3-(4-lluoropheny/carbamoyl)-phenylj-amide. Prepared as in Example 1 from 1-ethyl-5-(2-methyl-f1.3)dioxolan-2-yl)-2-oxo-2,3-dihydro-1H-indole-3-carboxylic acid methyl ester and 3-emino-N-(4-fluoro-phenyl)-benzamide. Rocrystallized from ethyl acetate - hexanes - benzene. Cacculated for C<sub>26</sub>H<sub>22</sub>FN<sub>3</sub>O<sub>2</sub>: C 67.87; H 4.83; N 9.15; found C 88.34; H 8.3; N 8.80.

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Example 6

[0052]

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[0033] <u>5.4cetyk-1-ethyt-2-oxo-2,3-dihydro-1H-indote-3-carboxylic acid [3-{4-ethylphenylcarbamoyl-phenyll-amide.</u> Propeted as in Example 1 from 1-ethyl-6-{2-methyl-1/3|dioxaba-2-yh-2-oxo-2,3-dihydro-1-Hindote-5-acrboxylic acid methyl ester and 3-emino-4-(4-ethyl-phenyl-bertzeinle, Purlified by chromatography (chloroform/methanol, 10:1). <sup>1</sup>H NMR (DMSO-d8) 5 1.15 (m, 6 H), 2.5 (q, 2 H), 3.85 (q, 2 H), 6.85-8.3 (m, 11 H), 10.0 (e, 1 H), 11.1 (e, 1 H).

Example 7

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25 [0054]

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40 [0055] 5-Acetyk1-sthyt2-oxo-2,3-dihydro-1H-indole-3-carboxylic acid [3-(3-fluorophenylcarbamoyl)-phenyl-amide. Prepared as in Example 1 from 1-ethyt-5-(2-methyt-1,3)dioxolan-2-yl)-2-oxo-2,3-dihydro-1H-indole-3-carboxylic acid methyl ester and 3-amino-N-(3-fluoro-phenyl)-benzamide. ¹H NMR (CDCl<sub>3</sub>) § 1.25 (t, 3 H), 2.6 (s, 3 H), 3.85 (q, 2 H), 4.45 (s, 1 H), 6.85-8.05 (m, 11 H), 8.3 (s, 1 H).

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Example 8

[9026]

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[0057] 5-Acatyl-1-ethyl-2-oxo-2,3-dihydro-1H-indole-3-carboxylic acid [3-(4-bromophenylcarbamoyl)-phenyl]. amide. Prepared as in Example 1 from 1-ethyl-5-(2-methyl-1,3|dixxolan-2-yl)-2-oxo-2,3-dihydro-1H-indole-3-carbox-ylic acid methyl ester and 3-amino-N-(4-bromo-phenyl)-benzamide. mp 117-120°C.

Example 9

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[0058]

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[0059] S.Acetyt-tethyl-2.oxo-2.3-dihydro-1H-indole-3-carboxylic acid [3/4-iodopheny/carbamoyl)-phenyfl-amido. Prepared sa if Example 1 tron 1-simyle-2/2-methyl-1; 3/dioxolan-2-yly-2-oxo-2,3-dihydro-1H-indole-3-carboxylic acid methyl ester and 3-amino-N-(4-iodo-phenyf)-benzamide. mp 205-210 °C. Calculated for C<sub>26</sub> H<sub>28</sub>IN<sub>3</sub>O<sub>4</sub>: C 55 O4; H 3.91; N 7.41; found C 55.13; H 4.04; N 7.12.

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[0900]

[0061] 5-Benzoyl-1-ethyl-2-oxo-2,3-dihydro-1H-indole-3-carboxylic acid (3-phenylcarbamoylphenyl)-amide. Prepared as in Example 1, Step A, from 5-benzoyl-1-ethyl-2-oxo-2,3-dihydro-1H-indole-3-carboxylic acid ethyl ester (US 4,886,224) and 3-amino-N-phenyl-benzamide. Purified by trituration in ethyl acetate / hexanes.mp 129-135°C.

Example 11

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[0062]

[0063] 5-Benzoyf-1-ethyl-2-oxo-2-3-dibydro-1H-indole-3-carboxylic acid [3-(4-bromophenylcarbamoyl)-phenyl]. esting, Prepared se in Example 1, Stop A, from the Shenzoyf-1-ethyl-2-oxo-2,3-dibydro-1H-indole-3-carboxylic acid shiyl ester (US 4, 586,224) and 3-amino-N4-bromo-phenyl-benzamide. Purlind by flash-chromatography (hexanes / acetone, 1:1) followed by inturation in ethyl acetate / hexanes.mp 139-142°C.

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Example 12

[0064]

[0055] <u>5-Acetyl-1-methyl-2-oxo-2-3-dihydro-1H-indole-3-carboxylic acid (3-phenylcarbamoylphenyl)-amide.</u> Propered as in Exempire I from 1-methyl-8(2-methyl-1) aldoxolar-2-yl)-2-oxo-23-dihydro-1H-indole-3-carboxylic acid mo-thyl ester and 3-amino-N-phenyl-benzanide. Purlified by Irituration in haxanase/aithyl acetate. mp 178-179 °C. Cabulated for C<sub>22</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>: C 70.25; H 4.95; N 9.83; found C 69.89; H 4.79; N 9.69.

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Example 13

[0000]

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[0067] 5-Acetyk-1-methyk-2-oxo-2,3-dihydro-1H-indole-3-carboxykc\_acid\_[3-(4-bromophenytcarbamoyt)-phenyl]. amide, Prepared as in Example 1 from 1-methyk-5-(2-methyk1,3)dioxolan-2-yi)-2-oxo-2,3-dihydro-1H-indole-3-carboxylic acid methyl ester and 3-emino-N-(4-bromo-phenyl)-benzamide. Purifiad by flash-chromatography (hexanes / sections, 1:1).

mp 234-236 °C. Calculated for C<sub>23</sub>H<sub>20</sub>BM<sub>3</sub>N<sub>3</sub>O<sub>4</sub>: C 59.30; H 3.98; N 8.30; found C 59.12; H 4.15; N 8.08.

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Example 16

[0072]

Example 14

[0068]

[0069] 1-Efthyt-2 ozo-5-propionyl-2,3-dihydro-1H-indole-3-carboxylic acid (3-phenytcarbennoyl-phenyl)-emide. Prepared as in Example 1 from 1-eithyl-5-(2-ethyl-1, 3)dioxolan-2-yl)-2-oxo-2,3-dihydro-1H-indole-3-carboxylic acid mophy toste and 2-amino-N-phenyl-benzamide. Purified by flash-chromatography (chloroform/methanol, 20.1) followed by trituration in hoxanes / ethyl acetate.mp 179-180 °C. Celculated for C<sub>27</sub> H<sub>28</sub> N<sub>3</sub> O<sub>4</sub>, C 71.19; H S.S3, N 9.22; found C 70.79; H S.73, N 8.79.

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Example 15

[000]

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[0071] 5-Oyclopentanecarbonyl-1-ethyl-2-oxo-2,3-dihydro-1H-indole-3-carboxylic acid (3-phenylcarbamoyl-phenyl)-amilda. Prepared as in Example 1 from 5-{2-cyclopentyl-1,3|dioxolan-2-y|}-1-ethyl-2-oxo-2,3-dihydro-1H-indole-3-carboxylic acid ethyl ester and 3-amino-N-phenyl-benzamida. Purified by flash-chromatography (haxanas / acctona, 1:1) followed by trituration in ethyl acetate mp 208-213 °C.

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[0073]

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Preparation 1

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[0074]

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1-ethyl-5-(2-methyl-1; 3)dioxolan-2-yi)-1,3-dihydro-indol-2-one (U.S. Pat. No. 4,686,224, 9.2 g, 37 mmof). The mixture was heated to reflux for 70 hours, then cooled, concentrated to about 25 ml., diluted with water, acidilied to pH 7 with acatic acid and extracted twice with ethyl acatate. The combined extracts were washed with brine, dried over magne-slum sulfate and concentrated in vacuo to an oily solid which was triturated in isopropy! ether, collected and dried to [0075] 1-Ethyl-6-(2-mathyl-[1,3|dioxolan-2-yf)-2-oxo-2,3-dihydro-1H-Indole-3-carboxylic acid methyl ester. Sodium (2.68 9, 112 mmol) was added to methanol (110 mL) in a 3-neck flask fifted with a reflux condenser, while controlling the temperature with an icebath. After dissolution, dimethyl carbonate (9.4 ml., 112 mmol) was added followed by furnish 7.9 g (70%) of product.

Preparations 2-4

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[0076] The compounds of Preparations 2 to 4 were prepared from the appropriate starting materials in a manner analogous to the method of Preparation 1. 55

Preparation 2

[0077] 1-Methyl-5-(2-methyl-(1,3)dioxolan-2-yl)-2-oxo-2,3-dihydro-1H-Indole-3-carboxylic acid methyl ester. Pre-pared from 1-mothyl-5-(2-methyl-(1,3)dioxolan-2-yl)-2,3-dihydro-indol-2-ono, which was propered as disclosed in U.S. Pat. No. 4,686,224.

Preparation 3

[0078] 1-Ethyt-5-(2-ethyl-11,3)dioxolan-2-yl)-2-oxo-2,3-dihydro-1H-indole-3-carboxylic acid methyl ester. Prepared from 1-ethyl-5-(2-ethyl-11,3)dioxolan-2-yl)-2,3-dihydro-indol-2-one, the title compound of Preparation 22. 5

Preparation 4

[0079] 5-(2-Cyctopentyl-[1,3]dioxolan-2-yl)-1-ethyl-2-oxo-2,3-dilydro-1H-Indole-3-carboxylic acid ethyl ester. Pre-pared from 5-(2-cyctopentyl-[1,3]dioxolan-2-yl)-1-ethyl-2,3-dilydro-Indol-2-one, the title compound of Preparation 24 5

Preparation 5

[0080]

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[0081] 3-Nitro-N-phenyl-benzamide. To a cooled (0°C) solution of entitine (17 g, 180 mmol) and triethylamine (27 mL, 180 mmol) in dichloramethane (100 mL) was added a solution of 3-hitrobenzoyl chloride (30 g, 180 mmol) in dichloramethane (100 mL). The mixture was sittred for 15 min at 0°C then overnight at room temperature. It was then poured into saturated sodium behabonate (1 L) and stirred vigorously for 15 min. The procipitate was collected, washed with water and dried (40 g, 100%).

Preparation 6

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[0082]

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[0083] 3-Amino-N-phenyl-benzamide, 10% Palladium on carbon (2.0 g) was added to a solution of 3-nitro-N-phenyl-benzamide (20 g, 83 mmol) in ethanol (225 mL) and the mixture was hydrogenated at 45 psi for 2 hours. The mixture was filtored through diatomacoous earth and concentrated to give a colonless solid (mp 118-120°C, 15 g, 90%).

Preparations 7-15

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[0084] The compounds of Preparations 7 to 15 were prepared from the appropriate commercially available starting

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materials in a manner analogous to the methods of Preparations 5 and 6 performed sequentially.

Preparation 7

[0085] 3-Amino-N-cyclohexyl-benzamide

Preparation 8

[0086] 3-Amino-N-(4-chloro-phenyi)-benzamide

Preparation 9

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[0087] 3-Amino-N-(p-tolyi)-benzamide

Preparation 10 5 [0088] 3-Amino-N-(4-fluoro-phenyl)-benzamide

Preparation 11

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[0089] 3-Amino-N-(4-ethyl-phenyl)-benzamide

Preparation 12

[0090] 3-Amino-N-(3-fluoro-phenyl)-benzamide

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Preparation 13

[0091] 3-Amino-N-(4-bromo-phenyl)-benzamide

Preparation 14

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[0092] 3-Amino-N-(4-lodo-phenyi)-benzamide

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[0093] 3-Amino-N-(3-methyl-phenyl)-benzamide

Preparation 16 9

[0094]

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washed with hexane and suspended in hexamethylphosphoramide (200 mL). Isalin (68.4 g, 0.20 mb)) was added carefully. After the gas evolution subsided, 2.22-trifluoroathyl locide (48.5 g, 0.22 mb) was added and the mixture was heated to 55°C for 4 hours. The solution was cooled, diluted with water (1 L), and the precipitate was collected. The filtrate was acidified with 6 N HCl and a new procipitate formed and was collected. The combined solids were recrystalized from 95% eithenol. Yield 22.5 (49%),mp 161-163 °C: 1-(2,2,2-Trifluoro-ethyl)-1H-indote-2,3-dione. Sodium hydride (8.65 g of a 60 % oil dispersion, 0.22 mol) was [0095] 8

Preparation 17

[9600]

[0037] 1-[2,2,2-Trilluoro-ethyl)-1,3-dihydro-Indol-2-one. A mixture of 1-(2,2,2-trilluoro-ethyl)1H-Indole-2,3-dione (9.2 g, 40 mmol) and 10% palladlum on carbon (2.4 g) in acetic acid (100 mL) and 70% prechloric acid (6.4 mL, 80 mmol) was hydrogenated in a Parr apparatus for 22 hours. The mixture was filtered through diatomacoous earth, diluted with water (1.5 L) and the precipitate was collected and dried. mp 155-162 °C. Yield 7.5 g (87%).

Preparation 18

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[869] 8

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[0099] 5-Acatyl-1-(2.2.2-trifluoro-ethyl)-1,3-dihydro-Indol-2-one. To a solution of 1 · (2.2,2-trifluoro-ethyl)-1,3-dihydro-indol-2-one (2.0 g. 8.3 mmol) and acopyl chloride (0.86 mL, 12 mmol) in carbon disutfiles (40 mL) was added aluminum trichloride (7.4 g. 56 mmol) proportions. The muture was hasted to reflux for 3 hours, then cooled. The liquid phase was decaniced and the residue was quenched carefully with loc, then water. The solids were filtered washed with water, defice and reccystalized from acctone/hexanes to give a pale pink solid, mp 170-171°C. Yield 1.23 g (51%).

Preparation 19

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fonc acid (10 mg) in benzene (25 mL) was heated to reflux for 4 hours in a flask fitted with a Dean-Stark trap. The solution was diluted with ethyl acetate, washed with saturated sodium bicarbonate, water and brine, dried over magnestim sulfate and concentrated in vacuo to an oil which solidified upon standing (1.19 g, 98%, mp 87-89°C). ro-ethyl)-1,3-dihydro-indol-2-one. A solution of 5-acetyl-1ethylene glycol (1.37 mL, 24 mmol) and p-toluenesul-[0101] 5-(2-Methyl-[1,3]dioxolan-2-yl)-1-(2,2,2-trifluo (2,2,2-trifluoro-ethyl)-1,3-dihydro-indol-2-one (1.04 g, 4 23

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Preparation 20

[0102]

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[0103] 3-[3,3-Diphenyl-ureido]-N-phenyl-benzamide, A mixure of 3-amino-N-phenyl-benzamide (2.0 g, 9.4 mmol), diphenyl-carbamoyl chloride (2.2 g, 9.4 mmol) and triethylamine (2.8 mL, 19 mmol) in ethanol (10 mL) was heated to reflux for 4.5 hours. The mixture was gooled and concentrated, water was added, the stury was acidified with 1 N HCI and the solid was collected, washed with water, dried and recrystallized from acetone / hexanes, to give a coloriess solid (1.63 g. 42%)

### Preparation 21

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[0104] 1-Ethyt-5-propkonyt-2,3-dihydro-Indol-2-one. Prepared from readily available starting materials (N-ethyloxin-dole and propionyl chloride) in a manner analogous to that set forth in Preparation 18. 23

#### Preparation 22

[0105] 1-Ehlyl-S-(2-ethyl-1,3]dioxolan-2-yl)-2,3-dilydro-indol-2-one. Prepared from the title compound of Prepara-tion 21 in a manner analogous to that set forth in Preparation 19. 8

#### Preparation 23

[0106] 5-Cyciopentanecarbonyl-1-ethyl-2,3-dihydro-indol-2-one. Prepared from readily available starting materials (N-ethyloxitndole and cyclopentanecarbonyl chloride) in a manner analogous to that set forth in Preparation 18.

#### Preparation 24

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[0107] 5-(2-cyclopenty-II.3]dioxolan-2-yi)-1-ethyl-2,3-dihydro-indol-2-one. Prepared from the title compound of repeatation 75 in a manner enalogous to that set forth in Preparation 19.
[0108] A particularity preferred subgroup of formula (III) compounds are those compounds selected from the group consisting of:

5-acetyl-1-ethyl-2-oxo-2,3-dlhydro-1H-indole-3-carboxylic acid (3-p-10h/icarbamoyl-phenyl)-amide;

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S-acety-1-ethyl-2-oxo-2,3-dihydro-1H-indole-3-carboxylic acid (3-(4-bromophenylcarbarnoyl-phenyl)-emide; and 5-acety-1-ethyl-2-oxo-2,3-dihydro-1H-indole-3-carboxylic acid (3-phenylcarbarnoyl-phenyl)-amide; the stereoisomers and prodrugs thereof, and the pharmaceutically acceptable salts of the compounds, stereolsomers, and [0109] The compounds of formula (IV), the stereoisomers and prodrugs thereof, and the pharmaceutically acceptable saits of the compounds, stereoisomers, and the prodrugs, may be prepared according to the following synthetic meth-8

and are illustrated by reaction schemes. Thase processes may be carried out in sequential or convergent synthetic Exemplary processes for the manufacture of the compounds of the general formula (IV) are provided below routes. Purilication procedures include crystaliization and normal phase or reverse phase chromatography. [0110] 55

[0111] As a general note, the preparation of the compounds of formula (IV) may also require protection of remote functionality (e.g., primary amine, secondary amine, carboxyl). The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. The need for such protection is

Scheme I

readity determined by one skilled in the art. The use of such protection/deprotection methods is also within the skill in the art. For a general description of protecting groups and their use, see T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York, 1991.

[0112] The following abbreviations are used herein.

min equiv DMSO dec CIMS DMF BOC CB2

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(IVa)

Scheme III

(IVb)

(Z)

(IVa)

(IVd)

Scheme V

Scheme VI

. X is a halogen

Base, Rb.X

RRNH

1. PhenylCHO, reduction

3. Exhaustive H2, Pd/C

2. NaCNBH<sub>3</sub>/ carbonyl compound

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## Scheme VIII

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15 [0113] The bicyclic pyrrolyl acids of Formula 5 can be made by several synthetic methods. With regard to Scheme I a preferred method (Hemesberger, H. et al., Monastheffe fur Chemie, 102: 184-204 (1972)), begins with condensation of an azido-acetic acid alkyl ester with an adelyded of Formula 2 in an alcoholic solvent in the presence of an alkoxide, Preferably, the alcohol and alkoxide and environment into corresponding alkyl ester to avoid transosterification.

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problems. The reaction is performed at a temperature of about -20°C to about 25°C for about 1·24 hours, generally employing 3-4 equivalent of the alkoxide and an equinal requirity of the azido-acetic acid ality aster. The resultant azides are then heated at reflux in an inext solvent such as a sylenes to addict the heterocyclopyrrole esters of Formula 3. An example of a utilable preparation is shown by Procedure H below.

The atdehydes of Formula 2 can be made by conventional methods known to those skilled in the art, or H. Heathcock, Ed., p 777), metal-halogen exchange of bromo- or lodohaterocycles (R" = Br.l) of Formula 1 or ildo.(Seo, D. Comins & S. P. Joseph In Encyclopadia of Reagents for Organic Synthosts Vol. 5, Wilay, New York, 1995, L. A. Paquetto, Ed., p 3503), reduction of heterocyclic esters of Formula 12 (R = alkyf) or ackds (R = H) to Formula 13 Organic Synthesis: Selectivity, Strategy & Efficiency in Modern Organic Chemistry Vol 7, S. V. Ley, Ed., Pergamon, genation of the aldehydes of Formula 14 using electrophilic halide sources such as A-halosuccinimide (R. M. Kellogg et at, J. Org. Chem., <u>3</u>2: 2902-2908 (1968)), *M*fluoropyridhium salls (Umemolo, T. et at, J. Am. Chem. Soc., <u>112:</u> 8563-75 (1990)), or elemental halogen (Oritz, J. A. et al., Eur. J. Med. Chem., <u>23</u>: 477-482 1988)). at., Eur. J. Med. Chem., <u>23</u>: 477-482 (1988)). With regard to Scheme II, exemplary preparations include Villsmeyer Haeck formytation of heterocycles (R\* = H) of Formula 1 (See, O. Meth-Cohn and S. P. Stanforth in Comprehensive Organic Synthesis: Selectivity, Strategy & Efficiency in Modem Organic Chemistry Vol. 2, Pergamon, New York, 1991, ithiation of heterocycles of Formula 1 (R\* = H) followed by treatment of heteroary lithiums of Formula 11 with a formylat Fleming, Ed., Pergamon, 1991, New York) such as lithium aluminum hydride, diisobutylaluminum hydride, or borane and subsequent oxidation of akcohols of Formula 13 to aldehydes of Formula 2 using oxidizing agents (Comprehensive 1991, New York) such as pyridinium chlorochromate, manganese dioxide, Swem reagent, and barlum oxide, or halo ing agent such as dimethylformamide (Ortiz, J. A. et al., Eur. J. Med. Chem. <u>23</u>: 477-482 (1988)) or N-methyl formani agents (Comprehensive Organic Synthesis: Selectivity, Strategy & Efficiency In Modern Organic Chemistry Vol 8, I methods for their preparation can readily be determined from the chemical literature (See, for example, Ortiz, J. A. e alcohols or aldehydes of Formula 2 (Nicolaou, K. C. et al., Angew. Chem. Int. Ed. Engl., 36: 168-7 (1997)) with reducin [0114] 9 5 8

H. et al., J. Heterocyclic Chem. 21: 785-9 (1984)). Other exemplary conditions useful for forming nitrites are described by R. Grashey in Comprehensive Organic Synthests: Selectivity, Strategy & Efficiency in Modem Organic Chemistry Alternatively, substitution of the heterocyclopyrroles of Formuta 3 can be accomplished by analogous conrentional methods known to those skilled in the art or substitution methods can readily be determined from the literature. For example, with regard to Scheme III, mono- and bis-halide substitution can be eccomplished by treatment with an electrophilic hatide source such as the Mhatosuccinimide, Mituoropyridinium salts, or elemental halogen (Gale, W W. et al., J. Org. Chem.,29: 2160-2165 (1964)) to produce heterocyclopymotes of Formula 4 (R; R" = H and/or hallde). Methyl substitution can be accomplished by Villsmeyer-Haack formylation to aldehydes of Formula 4 (R" =:CHO) In the prasence of zinc lodide in dichloroethane (C. K. Lau at. at., J. Org. Chem.,51: 3038-3043 (1964)). Mathyi and other alkyi substitution can also be accomplished by coupling Formula 3 bromo- or iodoheterocyclopyrroles (R = Br. i) (1996); G. M. Whitosides et al., J. Org. Chem., <u>52</u>: 2499-2496 (1988)), and alkonyl and alkynyl stannanes (Stille, J. K., Angew. Chem. Int. Ed. Engl., <u>25</u>: 508-524 (1986)) can also be coupled to the brome- or lodoheterocyclopyrroles of famao, D. W. Knight, and K. Sonogashira in Comprehensive Organic Synthesis: Selectivity, Strategy & Efficiency in Modern Organic Chemistry Vol 3 (Pergamon, New York, 1991, G. Pattenden, Ed., pp 435-551). Condensation of hy- CHO) can either directly (Ford R. E. et al., J. Med. Chem.,29, 538-549 (1985)) or after a second dehydration step (Mallcome, G. et al., Eur. J. Med. Chem. Chim.Ther. 28: 3-11 (1991) afford nitrites. Attematively, nitrite substitution can be accomplished by coupling to, palladıum chloride, dichlorobls(triphenyphosphine)palladıum (II), tetrakis(triphenyiphosphine)palladium (O), anc palladium acetate. Other exemplary conditions useful for forming carbon bonds to aromatic rings are described by K Vol 6 (Pergamon, New York, 1991, E. Winterfeldt, Ed., p 225). An example of a suitable nitrile preparation is Procedur followed by complete reduction of the formyl group under various reducing conditions such as sodium cyanoborohydrid and alkynes, in the presence of copper salts such as copper iodide (J. M. Tour et al., J. Org. Chem. 61: 6908-692 Formula 3 (R = Br, I) in the presence of a catalyst such as palladium. Palladium catalysts include, but are not limite cuprous cyanide to the bromo- or iodoheterocyclopyrroles of Formula 3 (R ~ Br, I) in dimethyllormamide (Klemm with alkyl metals such as alkyl copper reagents (Corey, E. J. et al., J. Am. Chem. Soc.89: 3911-12 (1967)). Alkei droxylamine with formylated esters of Formula 4 (R"=CHO) or acids of Formula 5 (R <u>e</u> 3 8 33 \$ ŧ

so [0116] Atternatively the aformentioned methods of substituting the heterocyclopyrnoles of Formula 3 can also be applied to the amindes of Formulae (IVs) and (IVb).

[0117] The coupling of an action formulae (Scheme I) with an amine of Formula A (Scheme IVI) or P (Scheme VIII) to furnish compounds of the general formula (IV) can be effected in several ways, which are analogous to those well

known to one of ordinary skill in the art.

[10178] In a typical coupling procedure, the acid and amine are combined with a suitable coupling agent. A suitable coupling agent that transforms the carboxylic acid group into a reactive species such that an amide inkage is formed between the carboxylic acid and the amine.

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[0119] The coupling agent can provide for the coupling in a one-pot process or several steps may be required to

we the coupling. Exemples of suitable coupling agents include 1-(3-dimetrydaminopropyl)-3-ethylcarbodiimide ochloride/hydroxybenzotriazole (DEC/HBT), carbonyldiimidazole, dicyclohexylcarbodiimide/ hydroxybenzotria zole, 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ), carbonyidiimidazole/ HBT, propanephosphonic anhysphosphonic acid anhydride, PAA) and diethylphosphorylcyanide.

[0120] The coupling reaction is generally parformed in an inert solvent, preferably an aprotic solvent at a temperature of about -20°C to about 50°C for about 1 to about 40 hours, optionally in the presence of a tertiary amine such as triethylamine. Suitable solvents include acetonitrile, dichloromethane, ethyl acetate, dimethylformamide and chloro

form, or mixtures thereof.
[0121] In an exemplary multistep coupling process, the carboxylic acid group is reacted with the coupling agent to form an activated intermediate, which can be isolated in the first step of the process. In a second step, the activated employ a small amount of dimethyfromarmide as a cosolvent with another solvent such as dichloromethane to catalyze the formation of the acid chloride. The acid chloride may be coupled with the amine in an appropriate solvent and a sultable base. Acceptable solvent/base combinations include dichloromethane, dimethyfroramide or accionitifie, or vents and temperatures are known to those skilled in the art and can be readily determined from the literature. These and other exemplary conditions useful for coupling carboxylic acids with aminos are described in Houben-Wayt, Vol. XV, part II; E. Wunsch, Ed. G. Thieme Vertag, 1974, Stuttgart, and M. Bodansky, Principles of Pepides Synthesis, Springer-Vertag Bertin 1984, and The Pepidess: Analysis, Synthesis and Blokogy (ed. E. Gross and J. Melenhofer), Vols 1-5 (Academic Press, NY 1979-1983). intermediate is then reacted with the amine to form the amide. Examples of coupling agents that convert an acld to an activated intermediate include thionyl chloride, oxalyl chloride, which form acid chlorides, cyanuric fluoride, which forms ecid flourides, or an alkyf chloroformate such as Isobutyl or Isopropenyl chloroformate (with a tertiary amine base). which forms a mixed anhydride of the carboxylic acid. If the coupling agent is oxalyl chloride, it is advantageous to nations include water or a C<sub>1</sub>-C<sub>5</sub> alcohol, or mixtures thereof, together with a cosolvent such as dichloromethane, tetrahydrofuran or dioxane, and a base such as sodium or potassium carbonate, sodium, potassium or lithium hydroxcatalyst (typically 1 to 10 mole %) such as a quatemary ammonium halida (e.g., tetrabutylammonium bromide or metryl trioctylammonium chloride) is advantagoous when a mixture of only partially miscible cosolvents is employed (e.g. mixture thereof in the presence of a tertiary amine base such as triethylamine. Other appropriate solvent/base combi ide, or sodium bicarbonate in sufficient quantity to consume the acid liberated in the reaction. Use of a phase transfer dichloromethane-water or dkhloromethane-methanof). Use of these coupling agents and appropriate selection of sol

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example, two common employed protecting groups are BOC, which is introduced by insating the arnho acid with di-fort-buy/disabonate, preferably in a profits aboven or a solvent mature at high pril, and CBZ, which is introduced by treating the amino acid with benzychroformatic, preferably in a protit solvent or a solvent mature, and a base. The amine-protected arnho acid with henzychroformatic, preferably in a protit solvent or a solvent mature, and a base. The amine-protected arnho acid intermediate of Formula B is then coupled with an appropriate amine of the formula HNRR, where the Riqueys are consistent with the compounds of the general formula (IV) in a procedure analogous to the coupling reaction set forth above to form a protected amide compound of Formula C. The protected amide of Formula C can then be deprotected to form an amide of Formula D. If the protecting group is BOC, the deprotection is typically [0122] The amines that are reacted with the carboxyric acid function group to make an amide of the present invention can be synthesized in a number of weys. With regard to Scheme IV, an alghbs amine acid of Fermiule A can be protected on the amine antiogen with an appropriate protecting group (P1) to form a protected amine acid of Fermiule B. The ability to readily select an appropriate amine protecting group is within the purview of one of ordinary skill in the art. For performed by treating the protected compound with an acid in an aprotic solvent. Suitable acids include HCI, CH3SO3H and trifluoreacetic acid. 8 ş 8

[0123] It may also be dastred to make esters of the compounds of Formula A or B. With regard to Scheme V, the esters of compound A and B can be made by reacting the compound with an appropriate alcohol and an acld catalyst such as concentrated surfuric acid or by treatment with an alkyl halide such as methyl idodide and a base such as potassium carbonate. Compounds of Formula E can also be mado by protocting a compound of Formula A, and then forming the ester. Alternatively, compounds of Formula E can be made starting with a compound of Formula A, forming an ester, and thon protecting the amine group. Analogous procedures for the formation and cleavage of esters and the protection of amine groups are well known to those skilled in the art.

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ing agant and a suitable base. Specific procedures for alkytation are described in Benoiton, Can. J. Chem. 55: 906-910 (1985), and Hanson, J. Org. Chem. 50: 945-950 (1977). For example, when PP is methyl, and Pr is BOC, sodium hydride and methyl iodide in tetrahydrofuran can be used. Deprotection of the compound of Formula B furnishes a [0124] According to reaction Scheme VI, the compounds of Formula A when Rb is not hydrogen can be prepared as follows. The Formula B amino acid can be prepared by N-alkylation of a compound of Formula G, which is an amine protected alpha amino acid. N-alkylation is well known in the art and can be accomplished using an appropriate alkylat

[0125] Altematively, a compound of Formula H can be N-alixylated by a three step sequence involving reductive benzylation, such as with benzaldehyde followed by Pd/C-catalyzed hydrogenation to give the mono-N-benzyl denv-

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anoborohydrids to introduce RP as methyl, to give the N-benzyl, substituted amino acid. The N-benzyl protecting group conveniently removed, for example, by hydrogenation with an appropriate catalyst, to yield a compound of Formula Specific conditions for the three step alkylation procedure are described by Reinhold et al., J. Med. Chem., 11: [0126] While many of the alpha amino acid starting materials are known, they can be synthestzed by a number of procedures that are well known in the art. For example, the Strecker synthesis or variations thereof can be used. noted that the aldehyde selected is determined by the destred amino add. The aminontitie is then hydrolyzed with a minoral acid to form the destred amino acid. Atternativery, the Bucherar-Berg method may be used where a hydanioin Accordingly, an aldehyde, sodium or potasstum cyanide and ammonium chloride react to form an aminonitrile. It is is formed by heating an aktehyde with ammonium carbonate and potassium cyanide followed by hydrolysis, for exam ple, with bartum hydroxide in refluxing dioxane, with acid or base to form the desired compounds. [0127] Sultable methods for the switheate and/or mand in the desired compounds. 5

acids) are found in reviews by Duthaler, Tetrahedron, <u>50</u>: 1539-1650 (1994), or by Williams, Synthesis of Optically Activo Amino Acids, Pergamon, Oxford, U.K. 1899. An altemative mathod is disclosed in Coroy and Link, J. Am. Chem. Sultable methods for the synthesis and/or resolution of compounds of Formula H (Scheme VI) (alphe amino Soc., 114: 1906-1908 (1992). 2

The synthesis of the compounds of formula (IV) where Y is [0128]

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by an appropriate depression and an articles are compared in the formula L. For example, if the protecting group is BOC. The Formula L compound is directly formed from the Formula K compound, and addition of water is not necessary. The Formula L compound can be protected on the nitrogen to form a compound of Formula M followed by hydrolysis of the ester with aqueous alkali at a temperature of about 0°C to about 5°C to a reaction-lent solvent resulting in the corresponding hydroxy setial of Formula M. The hydroxy acid of formula N is coupled to a suitable armine to from the protected armine to form the protected armine to form the protected armine to form the protected armine or Formula O. An enablogous may be accomplished by the coupling of an amide compound of Formula P (Scheme VII) with a bicylic pyrrolyl carboxylic acid of Formula 5. The procedure for the coupling can be carried out as described above. The synthesis of the amides of Formula P is Illustrated by Scheme VII. Initially, a nitrogen-protected amino aldehyde of Formula J is treated with example of the conversion of a Formula K compound to the corresponding Formula L compound is provided in PCT Application Publication No. WO/9325574, Example 1a. Other analogous examples where a cyanohydrin is converted to a Formula M compound can be found in U.S. Pat. No. 4,814,342 and EPO Application Publication No. 0 438 233. potassium or sodium cyanida in aqueous solution with a co-eolvent such as dioxane or ethyl acetate at a temperature of about 0°C to about 50°C to provide a compound of Formula K, which is cyanohydrin. The cyanohydrin of Formula K is then reacted with an alcohol such as methanol and a strong acid catalyst such as HCI at a temperature of about O°C to about 50°C, followed by the addition of water, if necessary. The protecting group is then removed, if still present, [0129] It may be destrable to have a certain stereochemistry at the alpha and beta positions of the compounds of Formula P. (The alpha position is the carbon atom containing the hydroxyl group.) The desired stereochemistry can be obtained by the use of a single stereolsoment aldehyde of Formula J. The Formula K cyanohydrin can be prepared from the stereochemically pure aldehyde by treatment with sodium or potassium cyanide as described above while maintaining the stereochemistry of the chiral carbon of the aldehyde, resulting in a mixture of stereoisomers, which can be separated, as is well known to those skilled in the art by crystallization. See, for axample, Blochemistry, 31: 8125-8141 (1992). Alternatively, isomer separation can be effected by chromatography or recrystallization techniques after conversion of a compound of Formula K to a compound of Formula L, M, N, O, or P by the procedures described herein and analogous to those well known in the art. g Ş 8

form a compound of Formula R. The compound of Formula R is reduced, for example, with disobutylaluminum hydride in hexane or foluene, or a mixture thereof, at a temperature of about -78°C to about -50°C followed by quenching with . With reference to Scheme VIII, the aminoaldehydes of Formula J can be made from the corresponding alpha amino acid of Formula Q. In one method, the alpha amino acid of Formula Q is protected on nitrogen and esterified to methanol at - 78°C as described in J. Med. Chem., 28: 1779-1790 (1985) to form the Formula J aldehyde. [0131] Attematively, the Formula J aldehydes can be made by oxidation of Formula T alcohols, for example, with [0130]

procedure described by Dickman et al., Organic Synthesis, Wiley: New York, 1890; Collect. Vol. VIII, p. 530. or with sulfuric acid-sodium borohydride by the procedure of Abiko and Masamuna, Tetrahedron Lett, 333: 5517-5516 (1992) or with sodium borohydride-lodine according to the procedure of McKennon and Myers, J.Org. Chem., 58: 3568-3571 cohols of Formula S. The Formula S aminoalcohols are prepared by the reduction of amino acids of formula Q. The reduction can be accomplished by treating Formula Q amino acids with lithium aluminum hydride according to the (1993), where other sultable procedures are also reviewed. The preparation of the alpha amino acid and N-alkylated pyridine-SO<sub>3</sub> at a temperature of about -10°C to about 40°C in a reaction-inert solvent, preferably dimethylsuffoxide alcohols of Formuta T, if not commercially available, can be made by the protection of aminoal alpha amino acids has been described above.

[0132] In addition, the aforementioned PCT Application Publication Nos. WO 96/3985 and WO 96/39384 contain further details and exemplifications of the processes of synthesizing aspects of the present compounds.

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## Equipment and General Procedures

on a Thomas Hoover capillary meting point apparatus. Uniess otherwise specified, reagents were used as obtained from commencial sources. The term "concentrated" refers to removal of solvent on a rotary evaporator. Exceptions in [0133] NMR spectra were recorded on a Bruker AM300 or Varian XL-400 spectrometer at about 23°C at 300 or 400 MHz, respectively, for proton nuckei. Unless otherwise specified, NMR spectral data is reported for a 400 MHz spec-trometer. Routine mass spectral data were obtained using a VG/Fisons instruments Platform il spectrometer operating with an Atmospheric Pressure Chemical Ionization (APCI) source. Melting points are uncorrected and were determined the use of the Procedures A-H are noted individually in parentheses, following mention of the procedure 2 8

## GENERAL SYNTHETIC PROCEDURES

Procedure A (Amide Formation Using 1-Hydroxybenzotriazole Hydrate and 1-(3-Dimethylamino-propy)-3-ethylcarbodiimide Hydrochloride) 23

[0134] A 0 °C 0.1-0.7 M mbture the primary amine (1 equiv, or a primary amine salt and 1 equiv of triethylamine per equiv HCl), 1 equiv of the specified carboxylic acid, and 1 equiv of 1-hydroxybenzotriazole hydrate (1 equiv relative to the carboxylic acid), in 3:1 dichloromethane:dimethylformamide is treated with 1 equiv 1-(3-dimethylaminopropyl)aqueous phase is oxtracted with eityl acetate. The combined organic phases are washed with saturated aqueous NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub>, and concentrated giving crude product which is purified by chromategraphy on silica gel 3-ethycarbodimide hydrochloride. The mixture is allowed to warm to room lemperature over several hours, slined overnight, concentrated to remove the dichloromethane, and partitioned between ethyl acetate and 1-2 N HCI. The and/or recrystallization 8 23

# Procedure B (Amide Formation Using 1-Hydroxy-7-azabenzoiriazole Hydrate and 1-(3-Dimethylamino-propy))-3-ethytcarbodimide Hydrochloride)

propyl)-3 ethycarbodlimide hydrochloride. The mixture is allowed to warm to room temperature over several hours, stirred overnight, and partitioned between ethyl acetate and 1-2 N HCl. The organic phase is washed with saturated [0135] A 0°C 0.1-0.3 M mixture of the primary amine or primary amine salt (1 equiv), 1 equiv of triethylamine, 1 equiv of the sactoxylic acid, and 1 equiv of 1-hydroxy-7-azabenzotriazole (1 equiv, relative to the carboxylic acid). in dimethytiormamide is treated with 1 equiv (corresponding in moi ratio to the carboxylic acid) 1-(3-dimethytaminoequeous NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub>, and concentrated giving crude product which is purified by chromatography on silica gel. \$ Ş

Procedure C (Amide Formation Using 1-Hydroxy-7-azabenzotriazole Hydrate and 1-(3-Dimethylamino-propy).

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[0138] A 0.3 M mixture of the primary amine hydrochloride (1 equiv), 1.2 equiv of triethylamine, 1 equiv of the specified carboxylic edd, and 1.2 equiv of 1-hydroxybenzotriazole hydrate in dimethyltormamide is treated with 1.2 equiv 1-(3-dimethylamino-propyl)-3-ethylcarbodimide methiodide. The mixture is stirred overnight and partitioned between ethyl acetate and 1 N NaOH. The organic phase is washed sequentlally with 1 N HCI and water, dried over MgSO<sub>4</sub> and concentrated giving crude product.

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allowed to cool to roam temperature, stirred overnight, and extracted with eithyl ecotate. The aqueous phase is exiditied with 2 N HCI and extracted with athyl acotate. The combined organic phases are dried over MgSO<sub>4</sub>, and concentrated A 0.1-0.8 M suspension of the ethyl ester (1 equiv) and KOH (2 equiv) in water is heated at reflux for 1-7 h, giving crude product which is purified by chromatography and/or washing with solvent.

# Procedure E (Hydrolysis of Ethyl Ester with Sodium Hydroxide)

A 0.1-0.8 M suspension of the ethyl ester (1 equity) and 2 N NaOH (10 equity) in methanol is heated at 65°C for 2 h, allowed to cool to room temperature, concentrated to remove the methanol, diluted with water, and extracted with ethyl acetate. The aqueous phase is acidified with 2 N HCI and extracted with ethyl acetate. The combined organic phases are dried over MgSO4, and concentrated giving crude product which is purified by recrystallization. 9

## Procedure F (Hydrolysis of Ethyl Ester with Lithlum Hydroxide) 5

[0139] A 0.1-0.3 M solution of the ethyl ester (1 equh) and LIOH-H<sub>2</sub>O (4-6 equh) in 3:2:1 tetrahydroturan:methanol: water is heated at 60-65°C overnight, allowed to cool to room temperature, concentrated to remove the tetrahydroturan and methanol, and aciditied with 1-2 N HCI. The resultant precipitate is filtered, washed with water, and dried *in vacuo* 8

# Procedure G (Nitrile Formation with Hydroxylamine Hydrochloride)

[0140] A 0.1-0.2 M mixture of the aldehyde (1 equiv) and hydroxylamine hydrochloride (2.2-4 equiv) in dimethyfror-manide is heated at 15-2° Covernight, allowed to cool to const morperature, and partitioned between eithyl accetate and water. The aqueous phase is cartacted with eithyl accetate. The compiled organic phases are washed with water, dried over MgSO<sub>4</sub>, and concentrated giving crude product which is purified by chromatography on altice get. 25

## Procedure H (Annulation with Azido-acetic Acid Ethyl Ester) 8

and azido-ecatic ecid ethyl ester (1 equiv relative 10 sodium) dropwise such that the reaction temperature was main-rished ast 5-10°C. The reaction mixture is strated for 1-2, quenched with color startared adqueous NH<sub>2</sub>C, and extracted with ether. The combined organic phases are dried over MgSO<sub>2</sub> and concentrated. The residue is purified by chroma-tography on silica gel. A 0.1-0.2 M solution of the resultant acrytate in xylenes is heated at reflux for 20-60 min and [0141] A 0°C 0.6-1.2 M solution of sodium (3-4 equiv) in ethanol is treated with a mixture of the aidehyde (1 equiv) allowed to cool to room temperature. The reaction solution is either cooled further to induce crystallization of the product or concentrated giving crude product which is purified by washing with hexanes and/or chromatography on silica gel.

#### Example 1

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6H-Thieno(2,3-b]pyrrole-5-carboxylic acid [(1S)-benzyl-3-((3R,4S)-dihydroxypyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-

amino-1-((3R,4S)-dihydroxy-pyrralidin-1-y)/-(2R)-hydroxy-4-phanyi-butan-1-one were coupled according to Procedure
Ad-(4dinnshylamino)pyrdino (0.1 equiv) also added to the reaction mixture); rmp 137-145°C; CIMS mio 430.2 (M+Y): 1H
NMR (DMSO-Q<sub>6</sub>) § 11.67 (br. s. 1H), 7.74 (d. J. = 8.9 Hz, H), 7.21 (m. 4H), 7.21 (m. 1H), 8.96 (s. 3H), 5.03 (dd. J =
2.9, 7.5 Hz, 0.5H), 4.93 (m. 1H), 4.97 (m. 0.5H), 4.80 (dd. J = 2.9, 7.5 Hz, 0.5H), 4.74 (br. s. 0.5H), 4.40 (br. s. 1H), 4.19
(m. 1H), 4.06 (dq. J = 3.2, 5.3 Hz, 0.5H), 3.99-3.87 (m. 1.5H), 3.54 (m. 1H), 3.38 (m. 0.5H), 3.25-3.06 (m. 2.5H), 6H-Thieno(2,3-b]pyrrole-5-carboxylic acid (Soth, S. et al., Bull. Soc. Chim. Fr., 2511-2515 (1975)) and (3S)-2.94-2.81 (m, 2H) [0142] ŧ 8

#### Example 1a

## [[1S]-Benzyl-3-[(3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxopropyl]-carbamic acid benzyl ester 55

[0143] (2R,3S)-3-Benzyloxycarbonylamino-2-hydroxy-4-phenyl-butyric acid (Taktia, T. et al., J. Med. Chem., 20: 510-515 (1977) and pyrrolidine-(3R,4S)-diol hydrochloride were coupled according to Procedure A (dimetryflormamide reaction solvent concentrated to ½ volume before work-up).

CIMS m/a 415.2 (MH\*); TH NMR (DMSO-4<sub>6</sub>) 8 7.28-7.15 (m, 10H), 7.07-7.01 (m, 1H), 4.94-4.75 (m, 4.5H), 4.65 (d, J = 7.7 Hz, 0.5H), 4.09-3.88 (m, 4H), 3.51-3.38 (m, 1H), 3.27-3.07 (m, 3H), 2.83-2.83 (m, 2H).

# (3S)-Amino-1-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-4-phenyl-butan-1-one

10% palladium on carbon (120 mg) in methanol (20 mL) was shaken under a hydrogen atmosphere (40-45 ps) on a Pan apparatus overnight, litered through Celite® , and concentrated. The product was obtained as a sticky solid (1.0 10144] According to a procedure by Takita, T. et al. (J. Med. Chem., <u>20</u>: 510-515 (1977)) a mixture of [(15)-benzyf-3-(381,45)-ditydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyil-carbamic acid benzyf ester (1.2 g, 2.9 mmol) and

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g, 100%). CIMS m/a 281.2 (MIH+); <sup>1</sup>H NMR (DIMSO-d<sub>g</sub>) 8 7.27-7.13 (m, 5H), 4.95-4.80 (m, 3H), 3.93 (br s, 2H), 3.83 (dd, J = 3.3, 9.1 Hz, 1H), 3.45-3.05 (m, 6H), 2.99 (dq, J = 3.5, 6.3 Hz, 1H), 2.65 (m, 1H), 2.50 (m, 1H)

#### Example 2

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2-Bromo-6H-thieno(2,3-b)pyrrole-5-carboxytic acid [(15)-benzyl-3-((3R,4S)-dihydroxypyrrolidin-1-yl)-(2R)-hydroxy-

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(ER)-hydroxy-4-phenybulan-1-one were coupled exording to Procedure A.

mp 143-145°C; CINIS mile 508 05510.0 (AH+); 'H NMR (DMSO-4<sub>6</sub>,) 5 11,72 (pt·s. 1H), 7.64 (d. J. = 9.1 Hz, 1H), 7.22

mp 143-145°C; CINIS mile 508 05510.0 (AH+); 'H NMR (DMSO-4<sub>6</sub>,) 5 11,72 (pt·s. 1H), 7.64 (d. J. = 9.1 Hz, 1H), 7.22

Hz, 0.5H; J, 4.75 (d. J. = 44 Hz, 0.5H;), 4.44 (m. 1H), 4.10 (m. 1H), 4.00-3.85 (m. 2H), 3.54 (m. 1H), 3.39 (dc, J. = 4.9, 12.64; 0.5 Hz), 3.15-3.06 (m. 1H), 2.94-2.81 (m. 2H), 2.15 [0145] 2-Bromo-6H-thieno[2,3-b]pyrrole-5-carboxylic acid and (3S)-amino-1-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-

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#### Example 2a

### 2-Bromo-6H-thleno[2,3-b]pymole-5-carboxyfic acid 8

Chem., 21: 215-217 (1984)) was hydrolyzed according to Procedure F. CIMS m/e 244 02245.0 ((M-H)+); 14 NMR (DMSO-4<sub>6</sub>) 8 12.66 (br.e., 1H), 12.10 (br.e., 1H), 7.22 (e., 1H), 8.87 (d, J = 2.1 [0146] 2-Bromo-6H-thieno[2,3-b]pyrrole-5-carboxylic acid ethyl ester (Eras, J.; Galvez, C.; Garcia, F., J. Heterocycl.

Example 3 Hz, 1H).

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# 2-Methyl-6H-thieno(2,3-b)pyrrole-5-carboxylic acid (((S)-benzyl,3-((3R,4S)-dihydroxypyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyl-amide ŝ

### (2R)-hydroxy-4-phany-butan-1-one hydrochloride were coupled according to Procedure A (1,5 equiv 1-hydroxyben-zorriazole hydrate, 1,1 equiv 1-(3-dimethylamino-propyl)-3-ethylcarbodilmide hydrochloride, 15:1 dichloromethane: dimathylformamida; combinad organic phasas washed with water prior to saturated aqueous NaHCO<sub>3</sub>); mp 154-157°C; CIMS m/o 442.2 ((M-H)¹); ¹H NMR (DMSO-d<sub>6</sub>) § 11.58 (m, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.22-7.10 (m, 5H), 6.86 (s, 1H), 6.04 (s, 1H), 5.03-4.73 (m, 3H), 4.38 (pr.s, 1H), 4.38 (m, 1H), 3.98-3.88 (m, 2H), 3.53 (m, 1H), 3.39-3.05 (m, 3H), [0147] 2-Methyl-6H-thieno[2,3-b]pyrrole-5-carboxylic acid and (3S)-amino-1-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2.90-2.83 (m, 2H), 2.38 (s, 3H), ţ

#### Example 3a 8

# 2-Methyl-6H-thleno[2,3-b]pyrrole-5-carboxylic acid ethyl ester

[0148] Using a procedure by C. K. Lau et. at. (J. Org. Chem., <u>51</u>: 3038-3043 (1986)), a mixture of 2-formyl-6H-thieno [2.3-bjpyrrobe-5-carboxylic acid ethyl ester (Soh), S. et at., Bull. Soc. Chim. Fr., <u>25</u>11-251 (1975); 500 mg, 2.24 mmol), a 251, (1.08 g, 3.36 mmol), and NBBH-5CN (1.08 g, 1.68 mmol) in definitionehiane (2.7 mm) was stirred for 7 days and quenched with saturated aqueous NH<sub>2</sub>C(2 CE mL). The resultant biphasic mixture was stirred for an additional 30 min, extracted with ethyl acetate, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The product was purified by Chromatoron-chro-23

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matography (3.2 hexanes:ether) and obtained as a white foam (233 mg, 50%); mp 107-109°C; CIMS m6 208.3 (MH\*); 'H NMR (CDCl<sub>3</sub>) 8 9.13 (br.s. 1th), 6.94 (s. 1th), 6.61 (s. 1th), 4.33 (q. J= 7.1 Hz, 2th), 2.48 (s. 3th), 1.38 (t. J= 7.1 Hz, 3H).

#### Ехапріе 35

## 2-Methyt-6H-thieno[2,3-b]pyrrote-5-carboxytic acid

[0149] 2-Methyl-8H-thleno[2,3-b]pymole-5-carboxylic acid ethyl ester was hydrolyzed according to Procedure E. mp 180-182°C dec.; CIMS m²o 180.1 ((M-4)\*y); ¹H NMR[DMSO-d₂) δ 12.36 (s, 1H), 11.93 (s, 1H), 6.77 (s, 1H), 6.66 (s, 1H), 2.40 (s, 3H), 1.36 (t, J = 7.1 Hz, 3H). 5

#### Ехатріе 3с

## [(1S)-Benzyt-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propy]carbamic acid terr-butyl ester 5

[0150] (2R.3S)-3-tort-Butoxycarbonylamino-2-hydroxy-4-pheny-butyric acid and pyrrolidine-(3R,4S)-diol hydrochlo-hide were copiled according to Procedure A (1.05 equiv Iriehylamine, 1.1 equiv carboxylic acid; 1.5 equiv 1-hydroxy-benzotriazole hydratie; 1.1 equiv 1-(3-dimethylamino-propyl)-3-ethylcarbodilmide hydrochloride; after dichloromethane removal, residue partitioned between ethyl acciate and 2 N NaOH; combined organic phases washed sequentially with 2 N HCI and saturated NaC). 20

## CIMS m/e 381 (MH+)

Example 3d

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# (3S)-Amino-1-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-4-phenyl-butan-1-one hydrochloride

[0151] To a 0°C solution of [(1S)-benzyl-3-((3R,4S)-dihydroxy-pyrrolldin-1-yl)-(2R)-hydroxy-3-oxo-propylj-carbamic sect ferr-buyl setter (1:1 9, 2.5 mmol) in methinoid (4 ml.) was added 4 to HCl in dioxane (2.7 ml., 28.8 mmol). The solution was allowed in solowy warm to room temperature and stirred overlight. The reaction mixture was concentrated and the residue was washed with methanoland dried in vacvo. The product was obtained as a white solid (1.03 g, 113%). CIMS m/e 281.2 (MH+).

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#### Example 4

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# (±)-2-Methyl-6H-thleno(2,3-b]pyrrole-5-carboxylic acid (1-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]

[0152] 2-Methyl-6H-thianol(2,3-b)pymole-5-carboxylic acid and (±)-2-amino-1-((3R,4S)-dhydroxy-pymolidin-1-yl)-3-phenyl-pomple-1-one hydrochloride were coupled according to Procedure A (1.5 equiv 1-hydroxybenzothazole hydroxyl-anzothazole hy 4.05-3.82 (m, 2.5H), 3.40-2.87 (m, 5.5H), 2.38 (s, 3H). \$ ŧ

# (±)-[1-Benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-carbamic acid tert-butyl ester

Boc-DL-Phenylalanine and pyrrolidine-(3R,4S)-diol hydrochloride were coupled according to Procedure A 1.5 equiv 1-hydroxybanzotriazola hydrate, 1.1 equiv 1-(3-dimethylamino-propyl)-3-ethylcarbodilmide hydrochloride, dichloromethane; 3 d reaction time). [0153] 8

CINS.π/e351.2 (MH·); ¹H NIMR (CDCL<sub>6</sub>),87.28-7.19 (m,5H),5.35 (m,1H),4.52 (m,1H),4.14.3.89 (m,1.5H),3.78-3.63 (m,1.5H),3.78-3.63 (m,1.5H),3.00-2.65 (m,3H),1.40 (s,9H).

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# (±)-2-Amino-1 -((3R,4S)-dihydroxy-pyrrolidin-1 -yl)-3-phenyl-propan-1-one hydrochloride

- ester (6.5 g, 20 mmol) in methanol (8 mL) was added 4 N HCI In dioxane (50 mL, 200 mmol). The solution was allowed and the precipitate was littered, washed with ether, and dried in vacuo The product was obtained as a white soild (5 To a 0°C solution of (±)-[1-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-carbamic acid *tert-*butyl to slowly warm to room temperature and stirred overnight. The resultant white reaction mixture was diluted with ether
- g, 87%). CIMS m/8251.2 (MH+); 'H NIMR (300 MH2, DMSO-4g) 8 8.28 (dp. 8, 3H), 7.38-7.21 (m, 5H), 5.11-4.93 (m, 2H), 4.34-4.22 (m, 1H), 8.36 (m, 1H), 8.81-3.70 (m, 1H), 3.89 (m, 0.5H), 3.47 (m, 0.5H), 3.33-2.85 (m, 4H), 2.63 (m, 1H). 9

#### Example 5

## 2-Bromo-6H-thieno[2,3-b]pyrrole-5-carboxylic acid ((1S)-benzyl-2-((3R,4S)-dlhydroxypyrrolldin-1-yl)-2-oxo-ethyll-5

3-phenyl-propan-1-one hydrochloride were coupled according to Procedure A (1.5 equiv 1-thydroxyberizotriazole hydrate, 1.1 equiv 1-thydroxyberizotriazole hydrate, 1.1 equiv 1-thydroxyberizotriazole hydrate, 1.1 equiv 0.1-thydramn-chinethylforma-mide; combined organic phases weshed with water prior to asturated aqueous NaHCO<sub>2</sub>); rp. 140-42°C; CIMS rave 477.3473; 9 (MH-Y); H-NRIC (NSN-C-6); 5 (1.75 e, 14), 8.55 (a, Je. 8.1 Hz, 14), 7.267.09 (m, 74), 5.00 (for a, 0.5H), 4.91.4.85 (m, 1.5H), 4.77 (m, 1H), 4.07-3.93 (m, 1.5H), 3.83 (m, 1.5H), 3.41-3.25 (m, 1H), 3.13 (m, 2H), 3.00-2.87 (m, 2-Bromo-6H-thieno[2,3-b]pyrrole-5-carboxylic acid and (2S)-amino-1-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-[0155]

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#### Example 5a

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# [(1S)-Benzyi-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-carbamic acid tert-butyl ester

- Boc-L-Phenylalanine and pyrrolidine-(3R,4S)-diol hydrochloride were coupled according to Procedure A (1.5 [0156] 8
- equiv 1-hydroxybenzotrazole hydrate, dichiloromethane; reaction mixture diluted with ethyl acetate and washed sequentially with 1 N NaOH, 1 N HCl, and saturated sodium chloride prior to drying).

  CIMS m/o 351.2 (MH\*); <sup>1</sup>H NNR (DMSO-Q<sub>3</sub>) 8 7.25.7.13 (m, 5H<sub>3</sub>) 7.06 (dd. J. = 8.4, 13.6 Hz. 1H<sub>3</sub>) 4.88 (d, J. = 5.0 Hz. 0.5H<sub>3</sub>) 4.81 (d, J. = 5.0 Hz. 0.5H<sub>3</sub>) 4.88 (d, J. = 8.5, 14.3 Hz. 1H<sub>3</sub>) 4.02 (m, 0.5H<sub>3</sub>) 3.94 (m, 0.5H<sub>3</sub>) 3.88 (dd. J. = 5.9, 10.1 Hz. 0.5H<sub>3</sub>) 3.38 (dd. J. = 5.3, 12.2 Hz. 0.5H<sub>3</sub>) 3.27-3.10 (m, 3H<sub>3</sub>) 2.83-2.67 (m, 2H<sub>3</sub>) 1.27 (s, 5H<sub>3</sub>) 1.25 (s, 4H<sub>3</sub>). 8

#### Example 5b

## (2S)-Amino-1-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-3-phenyl-propan-1-one hydrochloride \$

- 2-oxo-ethyl]-carbamic acid terr-butyl ester (27 g, 77 mmol). The solution was stirred 2.5 h and concentrated. The [0157] To 4 N HCl In dioxane (120 mL, 480 mmol) was added [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)
- product was obtained as a white solid (21.5 g, 98%).

  Max mez 25; (kM+1; H NMR (DMSO-44, 5 8.33 (br s, 3H), 7.32-7.16 (m, 5H), 5.10-4.86 (m, 2H), 4.25-4.13 (m, 1H), 3.93 (m, 1H), 3.73-3.66 (m, 1H), 3.54 (m, 0.5H), 3.46-3.23 (m, 1.5H), 3.18-3.05 (m, 2H), 3.00 (m, 0.5H), 2.81-2.78 (m, 1H), 2.57 (dd, J = 5.6, 1.00 Hz, 0.5H). ţ

#### Example 6

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# 2-Chloro-6H-thiono[2,3-b]pyrrole-5-carboxylic acid [(1.8)-benzyl-3-([3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyl-emide

[0158] 2-Chloro-8H-thleno[2,3-bjpyrrole-5-carboxylic acid and (35)-amino-1-((3R,45)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-4-phenyl-bultar-1-one hydrochloride were coupled according to Procedure A (1.5 equiv 1-hydroxyben-zotracole hydrate, 1.1 equiv 1-(3-dimethylamino-propy) 5-ethylcarbodinide hydrochloride, 25:1 dichloromathane: dimethylormanide; combined organic phases washed with water prior to saturated aqueous NaH-CO<sub>2</sub>), mp 148-162°C, CIMS m/e 464.04455.9 (MH-); 14 NMR (DMSO-4g, § 11.71 (m, 1H), 7.84 (d, J = 8.9 Hz, 1H), 7.23-6.98 (m, 7H), 2

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5.05-4.74 (m, 3H), 4.39 (m, 1H), 4.20 (m, 1H), 4.02-3.88 (m, 2H), 3.54 (m, 0.5H), 3.41-3.08 (m, 3.5H), 2.94-2.83 (m, 2H).

#### Example 6a

# \*0

[0159] Using a modified procedure by R. M. Kallogg et al. (J. Org. Chem., 33: 2902-290 (1968)), to a 0°C solution of 6H-thleno[2,3-b]pymole-5-carboxylic acid ethyl ester (Eras, J.; Galvez, C.; Garcla, F., J. Hetenocycl Chem., 21: 215-217 (1984); 1.45 g, 7.44 mmol) in acetic acid (15 mL) and CHO<sub>3</sub> (15 mL) was added M-chlorosucchinride (1.04 and then then then the product obtained was recrystallized using hoxanes/dicity/i ether (90:10). Last, the product of the recrystallization was further purified by flash column chromatography using 90:10 petroleum ether/sopropy/ ether. stirred overnight, concentrated to remove the chloroform, diluted with water, basifled with 5 N NaOH, and extracted with acetate. The combined organic phases were washed with saturated aqueous NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub>, g, 7.81 mmol) over 2 h. The reaction mixture was slowly allowed to warm to room temperature over several hours and concentrated. The product was purified by chromatron chromatography (radial) using 90:10 hexanos/diethyl ethe 5 5

The resulting product was obtained as a white solid (824 mg, 48%). CIMS n'e 228.2/230.2 ((M+H)\*); "H NMR (CDCL<sub>3)</sub> 5 9.28 (br.s., 1H), 6.38 (d. J = 1.9 Hz, 1H), 6.88 (s, 1H), 4.33 (q, J = 7.2 Hz, 2H), 1.35 (t, J = 7.2 Hz, 3H).

#### Example 6b

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## 2-Chloro-6H-thieno[2,3-b]pyrrole-5-carboxylic acid

[0160] 2-Chloro-6H-thleno[2,3-b]pymole-5-carboxylic acid ethyl ester was hydrohyzed according to Procedure D (reaction heated at 85 °C). 52

CIMS m'e 200.1/202.1 ((M-H)\*), <sup>1</sup>H NMR (DMSO-4<sub>6</sub>) § 12.86 (br.e., 1H), 12.08 (e., 1H), 7.11 (d., J = 1.9Hz, 1H), 6.88 (f. J = 2.1 Hz, 1H).

#### Example 7

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# 2-Chloro-6H-thleno(2,3-b)pymole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolldin-1-yj)-2-oxo-ethyfl

drate, 1.1 equix 1-13-dimethylamino-propyh-3-eithylcarbodiimide hydrochloride, 25.1 dichloromethano-dimothylfomae.
moist-combined organic phases washed with water prior to saturated equeous NaHCO<sub>3</sub>); mp 142-145°C; CIMS m/e
432.1454.2 ((M-H)?); H NINR (DMSO-Q) 3 11.2C (m, 11), 8.55 (d, J = 8.5 Hz, 11), 7.25.7; (m, 7H), 5.00 (d, J = 5.2 Hz, 0.5H), 4.994.70 (m, 2.5H), 4.992.776 (m, 2.5H), 4.902.776 (m, 2.5H 2-Chloro-6H-thieno[2,3-b]pyrrole-5-carboxylic acid and (25)-amino-1-((3R,4S)-dihydroxy-pyrrolidin-1-yl)propan-1-one hydrochloride were coupled according to Procedure A (1.5 equly. 1-hydroxybenzotriazole hy [0161] 33 \$

#### Example 8

# 2,4-Dichloro-6H-thieno[2,3-b]pyrrole-5-carboxylic acid [(1S)-benzyl-3-((3R,4S)-dihydroxy-pyrrolldin-1-yl)-(2R).

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dimethylformamide, 0.06 M); mp 130-134°C (dec.); CIMS n/e 496.2/498.2 ((M-H)\*); ¹H NMR (DMSO-4<sub>6</sub>), § 12.13 (br s, 1H), 7.40-7.15 (m, 7H), 5.51 (d, J = 5.8 Hz, 0.5H), 5.38 (d, J = 6.3 Hz, 0.5H), 4.99 (d, J = 4.9 Hz, 1H), 4.92 (d, J = 4.8 Hz, 0.5H), 4.85 (d, J = 4.1 Hz, 0.5H), 4.55-4.40 (m, 1H), 4.28 (m, 1H), 4.08-3.90 (m, 2H), 3.58-2.89 (m, 6H). [0162] 2,4-Dichtoro-6H-thleno[2,3-bjpyrrole-5-carboxylic acid and (3S)-amino-1-((3R,4S)-dihydroxy-pyrrolidin-1-yl)- (2R)-hydroxy-4-phenyl-butan-1-one hydrochloride were coupled according to Procedure A (1.5 equiv 1-hydroxyben-zotrazole hydrate, 1.1 equiv 1-(3-dimethylamino-propyl)-3-ethybcarbodiimide hydrochloride, 25:1 dichloromethane:

#### Ехатріе ва

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## 2.4-Dichloro-6H-thleno[2,3-b]pyrrole-5-carboxylic acid ethyl ester 55

[0163] To a 0°C solution of 6H-thiono[2,3-b]pymole-5-carboxylic acid ethyl ester (180 mg, 0.92 mmol) in acetic acid (2 mL) and CHCl<sub>3</sub> (2 mL) was added M-chlorosuccinimide (294 mg, 2.2 mmol) over 30 mln. The reaction mixture was

slowiny allowed to warm to room temperature over several hours, stirred overnight, concentrated to remove the chlo-roform, dituted with water, basified with S N NaOH, and extracted with ethyl acetate. The combined organic phases were washed with saturated aqueous NaHCO<sub>3</sub>, dried over MgSO<sub>2</sub>, and concentrated. The product was purified by Chromatron-chromatography (4:1 hoxanes-ethe) and obtained as a white solid (180 mg, 74%); mp 186-187\*C; CIMS me 262.1/264.1 ((M-H)-); 14 NMR (300 MHz, CDCl<sub>3</sub>) § 8.21 (br.e., 1H), 6.90.(s., 1H), 4.37 (q. J = 7.2 Hz, 2H), 1.39 (t. J = 7.2 Hz, 2H), 1.39 (t.

#### Example 8b

### 2,4-Dichloro-6H-thleno[2,3-b]pyrrole-5-carboxylic acid 5

2,4-Dichloro-6H-thieno(2,3-b]pyrrole-5-carboxylic acid ethyl ester was hydrolyzed according to Procedure E (reflux for 12 h before allowing to cool to room temperature; acidification with concentrated HCl; no purification). CIMS m/e 234.0/236.0 ((M-H)+); 14 NMR (DMSO-46) 8 12.28 (brs, 1H), 7.17 (s, 1H). [0164]

#### Example 9

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# (±)-4H-Thieno[3.2-b]pyrrole-5-carboxylic acid (1-benzyl-2-((3R,4S)-dihydroxypyrrolidin-1-yl)-2-oxo-ethyl)-amide

(1978)) and (‡)-2-amino-1-((3R,4S)-dihydroxy-pyrrolidin-1-yi)-3-phenyt-propan-1-one hydrochloride were coupled according to Procedure A (§:1 dichloromethan-edimethylformate), 0.08 M; combined organic phases washed with 2 N NaOH, dried over Na<sub>2</sub>SO<sub>2</sub>, in x p 212°C; CIMS me 400.1 (MM+1); 1 N NMF (DMSO-4<sub>0</sub>) 8 1.159 (m. 1-1), 8.1 (d. J = 8.5 Hz, 1-1), 7.30°T, 1 (m. 5+j), 8.82 (m. 1-j), 8.83 (m. 4H-Thieno(3,2-b]pyrrole-5-carboxylic acid (Soth, S.; Farnier, M.; Paulmier, C., Can. J. Chem. 56, 1429-34 [0165]

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#### Example 10

## 2-Вото-4H-thieno(3.2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-3-((3R,4S)-dinydroxypyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyli-amide 8

(2R)-hydroxy-4-phenyl-butan-1-one hydrochlodde were coupled excoding to Procedure 8 (1.5 equiv 1-hydroxy-7-aza-benzotriazole hydrate, 1.1 equiv 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride, 2S:1 dichloromethane dimethyllormemolic; reaction mixture stirred for 5 d, concentrated to remove dichloromethane before work-up; combined organic phasos washed with water prior to sturrated equent PALCO<sub>2</sub>; mp 138-142°C; CIMS m°c 508,05100 (AH+1); H NMR (DMSO-25, 51.188 (m, 14), 7.88 (d, J = 8.1 Hz, 14), 7.25-7.18 (m, 44), 7.12-7.08 (m, 24), 7.02 (s, 14), 5.05 (d, J = 7.5 Hz, 0.5H), 4.95 (m, 14), 4.88 (d, J = 5.0 Hz, 0.5H), 4.81 (d, J = 7.5 Hz, 0.5H), 4.75 (d, J = 3.5 Hz, 2-Bromo-4H-thieno[3,2-b]pyrrole-5-carboxylic acid and (3S)-amino-1-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-0.5H), 4.46-4.37 (m, 1H), 4.20 (m, 1H), 4.08-3.85 (m, 2H), 3.54 (m, 1H), 3.40·3.05 (m, 3H), 2.95-2.81 (m, 2H). [0166]

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#### Example 10a

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## 2-Bromo-4H-thleno[3,2-b]pyrrole-5-carboxyllc acid

Chem., 21: 215-217 (1984)) was hydrotyzed according to Procedure D (after cooling to room temperature, acidification with 2 N HCl; resultant precipitate filtered, suspended in toluene, concentrated; no purification).
CIMS m'e 244.0/246.0 ((M-H)\*); "H NMR (DMSO-4), § 12.63 (e, 1H), 12.04 (s, 1H), 7.13 (e, 1H), 6.97 (e, 1H). 2-Bromo-4H-thieno(3,2-bjpyrrole-5-carboxylic acid ethyl ester (Eras, J.; Galvez, C.; Garcia, F. J., Heterocycl [0167] ŧ\$

#### Example 11 8

# 4H-Thleno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-3-((3R,4S)-dihydroxypyrrolidin-1-yi)-(2R)-hydroxy-3-oxo-propyl}-amide

droxy-4-phenyl-butan-1-one hydrochloride were coupled according to Procedure A (combined organic phases washed with 2 N NaOH, dried over Na<sub>2</sub>SQ<sub>2</sub>); mp 185-190°C; CIMS m/e 430.1 (MH+); <sup>1</sup>H NMR (DMSO-C<sub>6</sub>) § 11.57 (e, 0.5H), 11.53 (e, 0.5H), 7.80 (d, J = 8.9 Hz, 1H), 7.32 (dd, J = 0.9, 5.3 Hz, 1H), 7.23 (m, 4H), 7.12 (m, 1H), 7.07 (s, 1H), 6.91 (3S)-arrino-1-((3R,4S)-dihydroxypyrrolidin-1-yl)-(2R)-hy and acid [0168] 4H-Thieno[3,2-b]pyrrole-5-carboxylic 55

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(m, 1H), 5.08 (d, J = 7.3 Hz, 0.5H), 4.96 (m, 1H), 4.89 (d, J = 5.2 Hz, 0.5H), 4.82 (d, J = 7.5 Hz, 0.5H), 4.76 (d, J = 4.2 Hz, 0.5H), 4.45-4.38 (m, 1H), 4.21 (m, 1H), 4.01-3.86 (m, 2H), 3.55 (m, 1H), 3.40 (dd, J = 4.9, 12.6 Hz, 0.5H), 3.23 (m, 1.5H), 3.17-3.07 (m, 1H), 2.97-2.83 (m, 2H).

#### Example 12

# (±)-2-Bromo-4H-furo[3,2-b]pyrrole-5-carboxylic acid (1-benzyl-2-((3R,4S)-dihydroxypyrrolidin-1-yl)-2-oxo-ethyll-

3-phenyl-propan-1-one hydrochloride were coupled according to Procedure A (1.1 dichloromethanic dinarylroman-mide; reaction mixture stirred for 3 d; combined organic phases weahed with Z N NaOH, dired over Na<sub>2</sub>SO<sub>3</sub>); m molo: reaction mixture stirred for 3 d; combined organic phases weahed with Z N NaOH, dired over Na<sub>2</sub>SO<sub>3</sub>); m mide; reaction mixture stirred for 3 d; combined organic phases weahed with Z NaOH, dired over Na<sub>2</sub>SO<sub>3</sub>); m 7.22-7.18 (m, 4H), Z 13 (m, 1H), 6.98 (1, J = 5.8 Hz, 1H), 6.89 (1, J = 0.8 Hz, 1H), 4.98-4.75 (m, 3H), 3.99 (m, 0.5H), 3.93 (m, 0.5H), 3.81 (m, 1.5H), 3.41-3.21 (m, 2.5H), 3.12 (m, 1H), 3.00-2.82 (m, 2H). (±)-2-amino-1-((3R,4S)-dihydroxy-pyrrolidin-1-yl)acid and 2-Bromo-4H-furo[3,2-b]pyrrole-5-carboxylic [6910] 5 5

#### Example 12a

## 2-Bromo-4H-furo[3,2-b]pyrrole-5-carboxyllc acid

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(4 equiv 2 N NaOH, enhanol; reflux 5h, room temperature overnight; after concentration to remove ethanol, residue partitioned between ethyl acetate and 2 N HCl; combined organic phases dried over Na<sub>2</sub>SO<sub>4</sub>, no purification); 'H NMR (DMSO- $\epsilon_0$ ) 5 12.47 (br s, 1H), 11.67 (s, 1H), 6.76 (d, J = 0.8 Hz, 1H), 8.67 (t, J = 0.8 Hz, 1H). Lesko, J.; Ferik, S., Collect. Czech. Chem. Comm., 46: 2564-2573 (1981)) was hydrołyzed according to Procedure E 2-Bromo-4H-furo[3,2-b]pyrrole-5-carboxylic acid ethyl [0170]

#### Example 13

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## 2-Bromo-4H-fura(3,2-b)pyrrola-5-carboxylic acid [(1S)-banzyl-3-((3R,4S)-dihydroxypyrrolidin-1-yl)-(2R)-hydroxy-8

formamide; reaction mixture stirred for 3 c; combined organic phases washed with 2 N NeOH, dried over Na<sub>2</sub>SO<sub>4</sub>); mp 112-123°C (doc.); CIMS mo 492-1494-1 (MH+); ¹H NMR (DMSO-c<sub>4</sub>) 8 11.31 (s, 0.5H), 11.27 (s, 0.5H), 7.71 (d, J = 8.7 Hz, 1H), 7.25-7.18 (m, 4H), 7.11 (m, 1H), 6.81 (s, 1H), 6.68 (d, J = 2.9 Hz, 1H), 5.05-4.73 (m, 3H), 4.44-34 (m, hydroxy-4-phenyl-butan-1-one hydrochloride were coupled according to Procedure A (2:1 dichloromethane dimethyl-2-Bromo-4H-furo[3,2-b]pyrrole-5-carboxylic add and (3S)-amino-1-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-1H), 4.17 (br s, 1H), 3.98-3.85 (m, 2H), 3.56-3.48 (m, 1H), 3.40-3.06 (m, 3H), 2.84-2.80 (m, 2H). [0171] 33

#### Example 14

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# 6H-Thieno(2,3-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxypyrrolidin-1-yf)-2-oxo-ethyl]-amlde

Na<sub>2</sub>SQ<sub>2</sub>); mp 179-184°C, CIMS m/e 400.1 (MH·); 398.2 ((M·H)·); 'H NMR (300 MHz, DMSO-d<sub>6</sub>) S 11.79 (br e 1H), 8.52 (d, J = 8.3 Hz, 1H), 7.34-7.16 (m, 6H), 7.04 (m, 2H), 5.04 (d, J = 8.1 Hz, 0.5H), 4.96 (d, J = 4.9 Hz, 0.5H), 4.90-4.80 propan-1-one hydrochloride were coupled according to Procedure A (1.5 equiv. 1-hydroxybenzoriazole hydrate, 1.1 equiv. 1-(3-dimethylamino-propy)-3-ethylcarbodimide hydrochloride, 15:1 dichloromethane:dimethyllormamide; reac tion mixture stimed for 3 d; after saturated aqueous NaHCO<sub>3</sub>, combined organic phases washed with water, dried over 6H-Thleno[2,3-b]pyrrole-5-carboxylic acid and (2S)-amino-1-((3R,4S)-dihydroxypyrrolldin-1-yf)-3-phenyt-(m, 2H), 4.09-3.98 (m, 1H), 3.89 (m, 1.5H), 3.49-3.29 (m, 2.5H), 3.19 (m, 1H), 3.08-2.91 (m, 2H) [0172] 45

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# 2-Bromo-4H-thieno(3,2-b)pyrrole-5-carboxylic acid [(15)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-

[0173] 2-Bromo-4H-thieno(3.2-bjpyrrole-5-carboxylic acid and (25)-amino-1-((3R,45)-dihydroxy-pyrrolidin-1-yl)-3-phenyt-propan-1-one hydrochloride were coupled according to Procedure A (1.5 equiv 1-hydroxybonzolrfazole hydrate, 1.1 equiv 1-(3-dimetrylamino-propyl)-3-ethylcarbodilmide hydrochloride, 25:1 dichloromethane-dimethylfroma-

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mder, reaction mixture affirmed for 3 cf. combined organic phases washed with water prior to saturated aqueous NaHCOs, adiade ore Na<sub>2</sub>SO<sub>4</sub>); mp 140–143°C; CIMS and «AZ6.14]; H NMR (300 MHz, DMSO-4<sub>4</sub>) S 11,73 (m. 1H). 8.61 (d. J. e 8.3 Hz, 1H), 7.34-7.18 (m. 6.H), 8.05-4.8 (m. 7.8), 3.04-2.95 (m. 5.5H), 3.46-2.95 (m. 5.5H).

#### Example 16

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# 2.Methyl-4H-thieno(3.2-b)pyrrole-5-carboxylic.gcid ((1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethylj-enide

mide; reaction mkture stirred for 3 c; combined organic phases washed with water prior to saturated equeous NaHCO, dried over Na<sub>2</sub>SO<sub>2</sub>); mp 128-130°C; CIMS me 412.2 ((M+H)¹), 414.1 (MH¹); ¹H NIMF (DMSC-cd<sub>2</sub>) § 1140 (m, 1H), 8.38 (m, 1H), 7.37-7.05 (m, eH), 6.65 (s, 1H), 4.97 (d, J = 5.2 Hz, 0.5H), 4.90-4.76 (m, 2.5H), 4.07-3.82 (m, 2.5H), 3.42-3.25 (m, 2.H), 3.13 (m, 1.5H), 3.01-2.87 (m, 2.H), 2.44 (d, J = 1Hz, 3.H). 3-phenyt-propan-1-one hydrochloride were coupled according to Procedure A (1.5 equiv 1-hydroxybenzotriazole hy-drate, 1.1 equiv 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride, 25:1 dichloromethans:dimethylformaand (2S)-amino-1-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-Methyl-4H-thleno[3,2-b]pyrrole-5-carboxylic acid [0174]

#### Example 16a

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## 2-Methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid ethyl ester 8

10175] 5-Methyl-2-thlophenecarboxaldehyde was annulated according to Procedure H (acrylate organic phases dried over Na<sub>2</sub>SO<sub>4</sub>

mp 129-130°C; CIMS mve 2082 ((M-H)\*), 210.2 (MH-H)\*; \*H NMR (CDCL), 8 8.90 (br s, 1H), 7.04 (s, 1H), 6.63 (s, 1H), 4.33 (q, J = 7.1 Hz, 1H), 2.54 (s, 3H), 1.36 (t, J = 7.2 Hz, 3H). 8

#### Example 16b

## 2-Methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid

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[0176] 2-Methyl-4H-thleno[3,2-b]pyrrole-5-carboxylic acid eithyl estler was hydrolyzed according to Procedure D (after cooling for come temperature, acidification with 2 N HCI, extracted with eithyl acetatis, organic phases dried over Na<sub>2</sub>SO<sub>6</sub>, no purification), CIMS mer 1902. ([M-H)\*\*), <sup>1</sup>H NMR (300 MHz, DMSO-G<sub>6</sub>) 8 12.35 (pr. s. 1H), 11.72 (s. 1H), 6.35 (s. 1H), 8.73 (s. 1H), 2.51 (s. 3H).

#### Example 17

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## 2,4-Dichloro-6H-thleno(2,3-b)pyrrole-5-carboxylic acid acid ((1S)-benzyl-24(3R,4S)-dihydroxy-pyrrolldin-1-yl)-2-oxoethyl]-amide

3-phenyt-propan-1-one hydrochloride were coupled according to Procedure A (1:5 equiv 1-hydroxybenzoritazole hydraction (1:5 equiv 1-(3-dimethylamino-propyl)-3-ethylcarbodilmide hydrochloride, 25:1 dichloromethane:dimethylroma-[0177] 2,4-Dichloro-6H-thieno[2,3-b]pymole-5-carboxylic acid and (2S)-amino-1-((3R,4S)-dihydroxy-pyrrolidin-1-yl) mide; 2 d reaction time; combined organic phases washed with water prior to saturated aqueous NaHCO3, dried ove Na<sub>2</sub>SO<sub>4</sub>). Ş

mp 203-204°C; CIMS mbe 468.1/470.1 (MH+); <sup>1</sup>H NMR (DMSO-4<sub>6</sub>) 5 12.20 (s, 1H), 7.55-7.58 (m, 1H), 7.28-7.08 (m, 6H), 5.04 (d, J = 3.3 Hz, 1H), 4.98-4.80 (m, 3H), 4.08-3.95 (m, 1H), 3.91-3.74 (m, 2H), 3.26-3.10 (m, 2H), 3.10-2.88 (H, 2H)

#### Example 18

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# 2-Суапо-6H-thieno(2,3-b)рутоle-5-саrboxylic acid [(1S)-benzyl-2-(3-hydroxy-azetidin-1-yf)-2-oxo-ethyf)-amide

[0178] 2-Cyano-6H-thieno[2,3-b]pyrrole-5-carboxylic acid and (2S)-amino-1-(3-hydroxyazetidin-1-yl)-3-phenyl-pro-8

pan-1 one hydrochloride were coupled according to Procedure B. CIMS rn'e 395.1 (MH\*); 14 NMR (DMSO-4<sub>6</sub>) 5 12.09 (s, 1H), 8.74 (d, J = 8.5 Hz, 1H), 7.99 (s, 1H), 7.29.7.12 (m, 6H), 5.68 (m, 1H), 4.58 (m, 1H), 4.41 (m, 1H), 4.28 (m, 0.5H), 4.11.3.90 (m, 2H), 3.69 (m, 0.5H), 3.57-3.49 (m, 1H), 3.01-2.88

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#### Example 18a

## 2-Cyano-6H-thleno[2,3-b]pymole-5-carboxylic acid

[0179] 2-Formyl-6H-thieno[2,3-b]pytrole-5-carboxylic acid (Soth, S. et al., Bult. Soc. Chim. Fr., 2511-2515 (1975)) state treated with hydroxylenine hydroxylenine hydroxylenine procedure G (100°C for 13 h, 125°C for 7 h; after cooling to room temperature, concentration, gave crude product; Commismore three, concentration, gave crude product; Coling me 190.9 ((M-H)\*); 14 NMR (DMSO-d<sub>6</sub>) 8 13.03 (br s., 14), 12.39 (br s., 14), 7.97 (s. 14), 7.04 (s. 14). 8

### Example 19

9

# 2-Chloro-6H-thieno[2,3-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-morpholin-4-yl-2-oxo-ethyl]-amide

[0180] 2-Chloro-6H-thleno(2,3-bjpyrnote-5-carboxylic acid and (2S)-amino-1-morpholin-4-yi-3-phenyl-propan-1-one hydrochloride (See, for example, Suzuki, K.; Fujila, H.; Sasaki, Y.; Shiratori, M.; Sakurada, S.; Kisara, K., Chem. Pharm. Buli, 3<u>6</u>, 4834-40 (1988)) were coupled according to Procedure C (solution of product in ethyl acctate washed with 5

water\_dried over MgSO<sub>4</sub>, concentrated). mp 108-110°C; CIMS m/e 416.3/418.2 ((M-H)\*); <sup>1</sup>H NWR (DMSO-d<sub>4</sub>) § 11.84 (m, 1H), 8.65 (d, J = 8.2 Hz, 1H) 7.39-7.13 (m, 7H), 5.08 (q, J = 7.6 Hz, 1H), 3.60-3.30 (m, 7H), 3.23 (m, 1H), 3.09-2.95 (m, 2H).

#### Example 20

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# 2-Chloro-6H-thieno[2,3-b]pyrrole-5-carboxytic acid [(1S)-dimethylcarbamoy1-2-phenyl-ethyl]-amide

fluoroacetate (See, for example, Holladay, M. et al., J. Med. Chem., 37: 630-5 (1994)) were coupled eccording to [0181] 2-Chloro-6H-thieno[2,3-b]pyrrole-5-carboxylic acid and (2S)-amino-N,N-dimethyl-3-phenyl-propionamide tri-53

Procedure C (product washed with ethyl scetate). mp 234-235°C; CIMS rule 374-29782 ((M-H)+); 'H NMR (DMSO-4<sub>6</sub>) § 11.72 (s, 1H), 8.53 (d, J = 8.1 Hz, 1H), 7.23 (m, 4H), 7.13 (m, 3H), 5.01 (m, 1H), 3.01-2.88 (m, 5H), 2.78 (s, 3H).

#### Example 21

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# 2-Chloro-6H-thiano[2,3-b]pyrrola-5-carboxylic acid [(1S)-benzyl-2-(1,1-dloxo-1-thiazolldln-3-yl)-2-oxo-ethyll-amide

propan-1-one hydrochloride (WO96/39384, Example 40a) were coupled according to Procedure C (solution of product in ethyl sectate weshed with water, dried over MGSQ, concentrated).

In appl sectate weshed with water, dried over MGSQ, concentrated).

IN 19.15-19.6 (m. 1H), 8.75 (dd. J = 81, 12.9, 141, 17.36 (m. 1H), 8.75 (dd. J = 81, 12.9, 141, 7.36 (m. 2H), 7.26-7.14 (m. 5H), 5.06-4.97 (m. 1H), 4.81 (m. 2H), 4.83 (d. J = 114, 0.5H), 4.55 (d. J = 12.5, 0.5H), 4.55 (m. 1H), 3.90-3.75 (m. 1H), 3.55-3.35 (m. 2H), 3.05 (m. 2H), 3.05 (m. 2H). [0182] 2-Chioro-6H-thieno[2,3-b]pymole-5-carboxylic acid and (2S)-amino-1-(1,1-dioxo-1-thiazolidin-3-yl)-3-phenyi 33

#### Example 22

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# 1-{(25)-{(2-Chloro-6H-thleno[2,3-b]pyrrole-5-carbonyl)-amino|-3-phenyl-propionyj-piperidine-4-carborylic acid ethyl ester

[0183] 2-Chloro-6H-thleno[2,3-bjpyrrole-5-carboxylic acid and 1-{(125)-amino-3-phenypropionyl)-pipendine-4-car-boxylic acid ethyl ester hydrochloride were coupled according to Procedure C (solution of product in ethyl acetato washed with water, dried over MgSO4, concentrated).

mp 104-105°C; CIMS m/e 486.2½488.2 ((M-H)<sup>3</sup>); <sup>1</sup> H NMR (300 MHz, DMSO-4<sub>6</sub>) § 11.84 (m, 1H), 8.64 (t, J = 8.8 Hz, 1H), 7.32-7.14 (m, 7H), § 10 (m, 1H), 4.30-3.89 (m, 4H), 3.15-2.82 (m, 3H), 2.80-2.50 (m, 2H), 1.89-1.69 (m, 2H), 1.52-0.94 (m, 5H). 8

#### Example 22a

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# 1-((2S)-tert-Butoxycarbonylamino-3-phenyt-propionyl)-piperidine-4-carboxylic acid ethyl ester

Boc-L-Phenylalanine (1.1 equiv) and piperidine-4-carboxylic acid ethyl ester were coupled according to Pro-[0184]

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oodure A (1.5 equiv 1-hydroxybenzatriazole hydrate, 1.3 equiv 1-(3-dimethylamino-propy)-3-ethylcarbodiimide hydro-chloride, room temperature, dichloromethane; reaction mixture poured into water, acidified with 1 N HCl; resultant chloride, room temperature, dichloromethane; reaction mixture poured into water, acidified with 1 N HCl; resultant procipitate filtered, filtrate extracted with CHCls, organic phase washed sequentially with water and brine, dried over MgSO, before concentration).

CINS me 465 2 (MH); <sup>1</sup>H NNR (CDCL<sub>3</sub>) 8 7.28-7.14 (m, 5H), 5.40 (dd, J= 8.9, 18.3 Hz, 1H), 4.82 (m, 1H), 4.34-24 (m, 1H), 4.08 (dq, J= 2.0, 7.1 Hz, 2H), 3.57 (m, 1H), 2.99-2.88 (m, 2.5H), 2.72 (m, 1H), 2.45-2.32 (m, 1.5H), 1.95-1.79 (m, 1.5H), 1.40 (d, J= 2.1 Hz, 9H), 1.23 (m, 3H), 0.88 (m, 0.5H).

#### Example 22b

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# 1-((2S).-Amino-3-phenyl-propionyl)-piperidino-4-carboxylic acid ethyl ester hydrochloride

[0185] To a solution of 1-((2S)-tert-butoxycarbonylamino-3-phenyl-propionyl)-plentidne-4-carboxylic acid ethyl ester (11 g, 27.20 mmol) in ethyl acetate (150 ml) was bubbled in HCl gas over 10 mln. The reaction mixture was stirred overnight, concentrated, redissolved in ethyl acetate and ether, and concentrated. The crude product was precipitated

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with hexanes, filtered, and dried in vacuo to give the title product (9.1 mg, 98%). CMS me 3051 (MH\*) HAMR (CDC<sub>0,1</sub>) 8 6.56 (for s. 211, 7.29.7.18 (m, 61), 4.94.482 (m, 11), 4.22.3.97 (m, 44), 3.53 (d<sub>1,1</sub>) = 4.55, 12.7.1 HJ, 3.14.27 (m, 114), 3.12 (m, 114), 2.95 (m, 0.51), 2.76 (t<sub>1,2</sub> = 10.9 Hz, 0.54), 2.66 (m, 0.54), 2.27 (m, 14), 2.07 (m, 0.54), 1.79-1.51 (m, 24), 1.39-1.1 (m, 3.51), 0.41 (m, 0.54)

#### Example 23

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# 2-Bromo-6H-thieno[2,3-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-(3-hydroxy-azetidin-1-yl)-2-oxo-ethyl]-amide

apan 1-one hydrochlorida wera coupled according to Procedure B. CIMS moe 448 1/450 (MH\*): THNMR (DMSO-04, 81 1.77 (e, 114), 8.55 (d, J= 8.1 Hz, 114), 7.26-7.10 (m, 714), 5.00-4.76 (m, 314), 4.07-3.94 (m, 1.514), 3.83 (m, 1.514), 3.40-3.22 (m, 114), 3.13 (m, 214), 2.38 (m, 214). 2-Bromo-6H-thleno(2,3-b)pyrrole-5-carboxylic acid and (2S)-amino-1-(3-hydroxyazetidin-1-yl)-3-phenyl-pro-[0186] 2

#### Example 24 8

# 2-Methyl-4H-turo[3,2-b]pyrrole-5-carboxylic acid ((1S)-benzyl-2-((3R,4S)-dihydroxypyrrolidin-1-yl)-2-oxo-ethyl]-amide

[0187] 2-Methyl 4H-Iuro[3,2-b]pyrrole-5-carboxylic acid (Krutosikova, A.; Kovac, J.; Dandarova, M.; Lesko, J.; Farlk, S., Collect, Czech. Chem. Comm., 46: 2564-2573 (1981)) and (25)-amino-1-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-3-phe-nyf-propan-1-one hydrochloride were coupled according to Procedure B (acidic aqueous phase extracted with ethyl acetate; organic phases combined prior to basic work-up). 8

CIMS mo 386.3 ((M-H)\*); H NIMF (DMSO-c<sub>6</sub>) § 10.86 (m, 1H), 8.23 (m, 1H), 7.27-7.18 (m, 4H), 7.14 (m, 1H), 6.83 (d, J = 5.4 Hz, 1H), 6.15 (s, 1H), 4.97 (d, J = 5.2 Hz, 0.5H), 4.89 (d, J = 4.6 Hz, 0.5H), 4.80 (m, 2H), 3.99 (m, 0.5H), 3.98 (m, 0.5H), 3.98

#### Example 25

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## 2-Trimethyslianylethynyl-6H-thleno(2,3-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-(3-hydroxy-azalidin-1-yl)-2-oxo-ethyl-amide Ş

[0188] Using a modified procedure of J. M. Tour et al. (J. Org. Chem., £1: 6306-6321 (1996)), to a degassed solution of 2-bromo-6H-thiano[2,3-b]pyrrole-5-carboxylic acid [(1S)-bonzy-2-(3-hydroxy-azatidin-1-yl)-2-oxo-ethyl-amide (106 mg, 0.24 mmol) in tetrahydrofuren (5 ml) was sequentially added diisopropyfamine (36 µl, 0.26 mmol), a mixture of copper(I) iodide (9 mg, 0.05 mmol) and dichlorobis(triphenythhosphine)paliadium(II) (68 mg, 0.1 mmol), and (trimeth-8

ysin/pacetylene (41 11, 0.29 mmd). The mixture was allined overnight, poured into water, and extracted with dichoromethane. The combined organic phases were washed with saturated NaCl, dried over MgSO<sub>Q</sub>, and concentrated. The product was purified by Chromatotron-chromatography (dichloromethane; 20:1 dichloromethane:methane) to give 8

the lite product (4.5 mg, 4%). CIMS me 464.3 ((M·H)?). <sup>1</sup>H NNR (DMSO-4<sub>6</sub>) 8 11.88 (s, 1H), 8.54 (t, J= 8.8 Hz, 1H), 7.31 (s, 1H), 7.23 (m, 4H), 7.13 (m, 2H), 5.66 (m, 1H), 4.56 (m, 1H), 4.41 (m, 1H), 4.28 (m, 0.5H), 3.57.3.46 (m, 1H), 2.99-2.85 (m, 2H), 0.23 (s, 8H).

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# 2-Ethynyl-6H-thleno(2,3-b]рутоle-5-carboxyllc acid [(1S)-benzyl-2-(3-hydroxyazetidin-1-yl)-2-oxo-ethyl]-amide

solution of 2-infmethylsllanylethynyl-6H-thleno(2,3-bjpyrnole-5-carboxylic acid [(1S)-benzyl-2-(3-hydroxy-azatidin-1-yl)-2-oxo-ethyll-amide (110 mg, 0.02 mmol) in methanol (0.5 ml) was added a 5% aqueous solution of potassium hydroxide (7 µL, 0.08 mmol). The reaction mbture was stirred for 3 h, concentrated to remove the methanol, dituted Using a procedure analogous to that of G. M. Whitesides et al. (J. Org. Chem.,53: 2489-2486 (1988)), to a of 2-trimethytsilanylethynyl-6H-thienof2,3-bjpymole-5-carboxylic acid [(1S)-benzyl-2-(3-hydroxy-azetidinwith water, and extracted with dichloromethane. The organic phase dried over MgSO4 and concentrated to give the title product (7 mg, 77%). [0189] . 5

CIMS me 392.1 (IA-H1)?; 'H NMR (CDCL), 8.72-7.16 (m, 7H), 7.03 (m, 2H), 4.66 (m, 1H), 4.47 (m, 1H), 4.17 (m, 1H), 4.00 (m, 1H), 3.75-3.56 (m, 3H), 3.35 (m, 1H), 3.04 (m, 2H).

#### Example 27

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# 2-Fluoro-4H-thieno[3,2-b]pyrrole-5-carboxylic acid ((1S)-benzyl-2-((3R,4S)-dihydroxypyrrolidin-1-yl)-2-oxo-ethyl]

3-phenyl-propan-1-ane hydrochloride were coupled according to Procedure B (4 d reaction time).

1728-713 (m, 6H), 6.71 (s, 1H), 4.99 (1, 3.5 E (M+r); Hind (DMSO-6), 8 1.172 (m; H), 6.49 (d. J. = 8.5 Hz, 1H), 728-713 (m, 6H), 6.71 (s, 1H), 4.99 (1, J. = 5.2 Hz, 0.5H), 4.91 (d. J. = 4.8 Hz, 0.5H), 4.86 (d. J. = 3.7 Hz, 1H), 4.79 (m, 0.5H), 3.94 (m, 0.5H), 3.84 (m, 1.5H), 3.42 (m, 2.5H), 3.14 (m, 1H), 3.01-2.84 (m, 2.H), 3.87 (m, 2.H), 3.88 (m, 1.5H), 3.42-3.24 (m, 2.5H), 3.14 (m, 1H), 3.01-2.84 (m, 2.H) 2-Fluoro-4H-thleno(3,2-b]pyrrolo-5-carboxylic acid and (2S)-amino-1-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-[0490] 8

#### Example 27a 52

## 2-Fluoro-4H-thleno[3,2-b]pyrrole-5-carboxylic acid ethyl ester

[0191] 5-Fluoro-thiophene-2-carbaldehyde (see, for example, Schuetz, R. D. and Nilles, G. P., J. Org. Chem., 36: 2188-90 (1971) was annulated according to Procedure H (aldehyde and azldo-acetic acid ethyl ester added as ethanol solution (0.6 M of ester); acrylate organic phase washed with saturated aqueous NaCl prior to drying; acrylate not purifie 8

CIMS m/e 212.1 ((M-H)+); 1H NMR (CDCs) 8 9.16 (brs, 1H), 7.03 (s, 1H), 6.51 (s, 1H), 4.33 (q, J= 7.2 Hz, 2H), 1.36 (t, J= 7.2 Hz, 3H)

#### Example 27b

33

## 2-Fluoro-4H-thieno[3,2-b]pyrrole-5-carboxyllc acid

[0192] 2-Fluoro-4H-thieno[3,2-b]pyrrole-5-carboxyfic acid ethyl ester was hydrolyzed according to Procedure F (acidified aquoous phase extracted with ethyl acetate, combined organic phases dried over MgSO<sub>4</sub>, concentrated). CIMS m'e 184.1 ((M+I'y); ¹H NMR (DMSO-4¢) S 12.47 (br.s. 1H), 12.03 (s. 1H), 6.96 (s. 1H), 6.73 (s. 1H). \$

#### Example 28

## 2-Cyano-4H-furo[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-(3-hydroxy-azetidin-1-yl)-2-oxo-ethyl]-amide \$

2-Cyano-4H-furo[3,2-b]pyrrole-5-carboxylic acid and (2S)-amino-1-(3-hydroxyazetidin-1-yl)-3-phenyl-propan-1-one hydrochloride were coupled according to Procedure B (reaction mixture partitioned between ethyl acetate and water prior to acidic washing). [0193] 8

CIMS me 377.1 ([M-H)+), 379.1 (MH+), <sup>1</sup>H NIMR (DMSO-d<sub>6</sub>) 8 11.78 (s. 1H), 8.68 (t.) = 8.2 Hz, 1H), 7.67 (s. 1H), 7.22 (m. 4H), 7.15 (m. 1H), 7.01 (d.) = 3.1 Hz, 1H), 5.68 (m. 1H), 4.59 (m. 1H), 4.40 (m. 1H), 4.26 (m. 0.5H), 4.05 (m. 1H), 3.00-2.88 (m. 2H).

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#### Example 28a

## 2-Cyano-4H-furo[3,2-b]pyrrole-5-carboxylic acid

[0194] 2-Formy/4H-furo[3,2-b]pymole-5-carboxylie acid (see, for example, Krutosikova, A.; Dandarove, M.; Alfoidi, J., Chem. Pap., 48: 268-73 (1994)) was treated with hydroxylamine hydrochloride according to Procedure G. CIMS m'e 174.9 ((M-H)\*); 'H NMR (DMSO-46,) § 13.10-12.50 (br s. 1H), 12.05 (s. 1H), 7.73 (s. 1H), 8.75 (s. 1H).

#### Example 29

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# 2-Chloro-4H-furo[3,2-b]pyrrole-5-carboxylic acid [(15)-benzyi-2-(131,4S)-dihydroxypyrrolidin-1-y1)-2-oxo-ethyj-amide

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[0195] 2-Chloro-4H-fura[3.2-b]pyrroie-5-carboxylic acid and (2S)-amino-1-([3R,4S)-dhydroxy-pyrroiidin-1-yl)-3-phenyl-pyrroian-1-one hydrochloride were coupled excording to Procedure B (3 d reaction time; reaction mixture partitionab bowene neityl acidate and water prior to acidic washing).

CIMS mo 418.1/450.1 (MHY): 'H NMR (DMSC) 13.36 (s, 1H), 8.42 (dd, J = 2.9, 8.3 Hz, 1H), 7.27-7.10 (m, 5H), 6.94 (d, J = 6.0 Hz, 1H), 8.83 (m, 1H), 4.99 (d, J = 5.2 Hz, 0.5H), 4.91 (d, J = 5.0 Hz, 0.5H), 4.86-4.77 (m, 2H), 4.00 (m, 0.5H), 3.94 (m, 0.5H), 3.94 (m, 0.5H), 3.93 (m, 1.5H), 3.43-3.21 (m, 2.5H), 3.13 (m, 1H), 3.00-2.85 (m, 2H).

#### Example 29a 8

## 2-Chloro-4H-furo[3,2-b]pyrrole-5-carboxylic acid ethyl ester

solution (0.8 M of ester); condensation reaction mixture allowed to warm to room temperature, stirred for 1 h, quenched at -40°C, diluted with water, and extracted with ether, acrylate not purified; crude furanopyrrole filtered before concen-[0196] 5-Chloro-furan-2-carbaldehyde (Snyder, H. R., Jr., Seahausen, P. H., J. Heterocycl. Chem., 10: 385-6 (1973)) was annulated according to Procedure H (8 equiv sodium; aldehyde and azido-acetic acid ethyl ester added as ethanol tration). 52

CIMS rive 212.0214.1 ((M+1)\*); 14 NMR (CDC4), 8 8.89 (br.e., 14), 6.74 (dd, J = 0.8, 1.7 Hz, 14), 6.31 (d, J = 0.6 Hz, 14), 4.33 (q, J = 7.1 Hz, 24), 1.36 (t, J = 7.1 Hz, 34). g

### Example 29b

## 2-Chloro-4H-furo[3,2-b]pyrroie-5-carboxylic acid

8

temperature overnight, 50°C 4 h; aciditied aqueous phase extracted with ethyl acetate; combined organic phases dried [0197] 2-Chloro-4H-furo[3,2-b]pyrroie-5-carboxylic acid ethyi ester was hydrolyzed according to Procedure F (room

over MgSQ<sub>4</sub>, concentrated). CIMS m'e 183.8/185.8 ((M+t)-); <sup>1</sup>H NMR (DMSO-4<sub>6</sub>) δ 12.47 (br s, 1H), 11.70 (s, 1H), 8.70 (s, 1H), 8.87 (s, 1H).

#### Example 30

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# 2-Chloro-4H-fura[3,2-b]pyrroie-5-carboxylic acid [(1S)-benzyl-3-((3R,4S)-dihydroxypyrroildin-1-yl)-(2R)-hydroxy-3-oxo-propyll-amide

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[0198] 2-Chloro-4H-Juro[3,2-b]pymoie-5-carboxylic acid and (3S)-amino-1-((3R,4S)-dihydroxy-pymolidin-1-yr);-(3R)-hydroxy-4-phenyl-bulan-1-one were coupled according to Procedure B (3 d reaction time; reaction mixture partitioned botween ethyl acetate and water prior to acidic washing).

CIMS me 448.1450.1 (MH-); 'H NNR (DMSO-44) S 11.33 (m, 1H), 7.72 (d, J = 8.7 Hz, 1H), 7.25-7.08 (m, 5H), 6.82 (H, 5H), 6.82 (H, 5H), 6.82 (J = 5.0 Hz, 0.5H), 4.80 (d, J = 7.3 Hz, 0.5H), 4.80 (m, 1H), 4.88 (d, J = 5.0 Hz, 0.5H), 4.80 (d, J = 7.3 Hz, 0.5H), 4.75 (d, J = 4.2 Hz, 0.5H), 4.454-4.35 (m, 1H), 4.18 (m, 1H), 4.09-3.88 (m, 2H), 3.57-3.49 (m, 1H), 3.39 (m, 0.5H), 3.28-3.08 (m, 2.5H), 2.95-2.80 (m, 2H). 8

#### Example 31

3

# 1-{(2S)-{(2-Chloro-6H-thieno[2,3-b]pyrrole-5-carbonyl)-amino]-3-phenyl-propionyl}-piperidine-4-carboxylic acid

[0199] 1-{(2S)-{(2-Chioro-6H-thleno[2,3-b]pyrrole-5-carbonyi)-amino]-3-phenyl-proplonyi]-piperidine-4-carboxyilc

22

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partitioned between ethyl acetate and 1-2 N NaOH; aqueous phase aciditied with 2 N HCI, extracted with athyl acetate; combined organic phases dried over MSSOL, concentrated; crude product washed with ather; mp 145-150°C; ¹H NMR (DMSO-42) 5 12.21 (s. 14), 1183 (s. 0.5H), 1177 (s. 0.5H), 858 (m. 14), 7.26-7.11 (m. 7H), 5.05 (m. 1H), 4.23 (d. J. = 13.3 Hz, 0.5H), 4.10 (d. J. = 12.6 Hz, 0.5H), 3.93 (d. J. = 12.7 Hz, 0.5H), 3.85 (d. J. = 13.5 Hz, 0.5H), 3.85 (d. J. = 13.5 Hz, 0.5H), 3.85 (d. J. = 13.5 Hz, 0.5H), 3.85 (m. 1H), 1.75-1.65 (m. 2H), 1.43-1.17 (m. 1.5H), 1.07-0.97 (m. 0.5H). acid ethyi ester was hydrolyzed according to Procedure F (room temperature;

#### Example 32

## 3-Chloro-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxypyrrolidin-1-yi)-2-oxo-ethyll-9

S-phenyl-propan-1-one hydrochloride were coupled according to Procedure B (reaction mixture partitioned between ply to east of water prior to actice washing).

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CIMS me 434.0438.0 (MH\*); 'H NWR (DMSO-4g, B 12.09 (m, 1H), B.57 (d, J = 8.3 Hz, 1H), 7.40 (m, 0.5H), 7.28-7.10 (m, 6.5H), 5.00 (d, J = 5.2 Hz, 0.5H), 4.92 (d, J = 5.0 Hz, 0.5H), 4.84 (m, 2H), 4.10-3.93 (m, 1H), 3.82 (m, 1.5H), 3.44-3.23 (m, 2.5H), 3.13 (m, 1H), 3.03-2.87 (m, 2H).

#### Example 32a

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## 3-Chloro-4H-thieno[3,2-b]pyrrole-5-carboxyfic acid ethyi ester

[0201] 4-Chloro-thiophene-2-carbaildehyde (infarte, J.; Martinez, E.; Muchowski, J. M., J. Heterocyci. Chem., 13: 383-4 (1976)) was annulated according to Procedure H (aldehyde and azido-acetic acid ethyl ester added as ethanol solution (1.2 M of esten) audo that reaction temperature maintained at 0°C; reaction mixture allowed to warm to 10°C, stirred for 1.5 h, poured into coid saturated aqueous NHz, Ci, after other extractions, combined acrylate organic phases washed with water until aqueous phase was neutral; acrylate not purified).

CIMS m/s 228.0 ((M-H)\*\*), 14 NNM (CDC\*\*), 5 9.02 (or s. 14), 7.24 (s. 14), 7.10 (s. 14), 4.37 (q. 1-7.1 Hz, 2H), 1.38 53

### (t, J= 7.1 Hz, 3H).

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#### Example 32b

## 3-Chloro-4H-thieno[3,2-b]pyrrole-5-carboxylic acid

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[0202] 3-Chloro-4H-thleno[3,2-bjpymole-5-carboxylic acid ethyl ester was hydrolyzed according to Procedure F (7 equiv LiOH-H<sub>2</sub>O; room temperature overnight, then at 50°C overnight again; acidified aqueous phase extracted with

ethyl acetate; combined organic phases dried over MgSO4, concentrated). CIMS m'e 199.9/201 8 ((M-H)\*); \*H NIMR (DMSO-4); § 12.71 (br.s., 1H), 12.40 (s., 1H), 7.48 (s., 1H), 7.06 (d., J = 1.9 Hz, 1H).

#### Example 33

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# 3-Chloro-4H-thleno(3,2-b)pyrrole-5-carbosylic acid ((1S)-benzyl-3-((3R,4S)-dlhydroxypyrrolldin-1-yl)-(2R)-hydroxy 3-oxo-propyll-amide

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[0203] 3-Chloro-4H-thleno(3,2-b)pyrrole-5-carboxylic ecid and (3S)-amino-1-((3R,4S)-dihydroxy-pyrrolidin-1-yf)-(2R)-hydroxy-4-phenyl-butan-1-one were coupled according to Procedure B (reaction mixture partitioned between ethyl

excitate and water prior to exidic weshing).

(III) This met asc. 60560 (M1) This M5O-46, 5 12.4 (m. 1H), 7.89 (d. J = 8.9 Hz, 1H), 7.38 (e. 0.5H), 7.28-7.10 (m. 5.5H), 7.05 (d. J = 5.1 Hz, 1H), 5.06 (d. J = 5.1 Hz, 1H), 5.07 (d. J = 5.1 Hz, 1H), 5.07

# 3-Bromo-4H-thieno[3,2-b]pymole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxypymolidin-1-yl)-2-oxo-ethyl]

3-Bromo-4H-thleno(3,2-b]pyrrote-5-carboxylic acid and (2S)-amino-1-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-3-phenyt-propan-1-one hydrochloride were coupled according to Procedure B (reaction mixture partitioned between [0204]

ethyl accitate and water prior to acidic washing). CIMS mod-87.54782 ((M-Hr)): H NMR (DMSC-46, 8 11.99 (m, 1H), 8.56 (d, J = 8.3 Hz, 1H), 7.48 (d, J = 1.2 Hz, 0.5H), 7.27-71.2 (m, 6.54), 4.89 (m, 2.14), 4.91 (d, J = 5.2 Hz, 0.5H), 4.84 (m, 2H), 4.96-3.82 (m, 1.5H), 3.78 (m, 1.5H), 3.43-3.22 (m, 2H), 3.13 (m, 1H), 2.99-2.85 (m, 2H), 5

#### Example 34a

### 3-Bromo-4H-thieno[3,2-b]pyrrole-5-carboxylic acid 2

allowed to warm to 10°C, stirred for 1 h, poured into coid saturated aqueous NH<sub>4</sub>C); after either extractions, combined excryste organic phases washed with water until aqueous phase was neutral; acrylate not purified). CIMS rive 272.0/273.9 ((M+H)+); <sup>1</sup>H NMR (CDCl<sub>2</sub>l) 8 8.99 (for e, 1H), 7.21 (s, 1H), 7.13 (d, J = 1.9 Hz, 1 H), 4.37 (q, J [0205] 4-Bromo-thipphene-2-carbaldehyde was annulated according to Procedure H (aldehyde and azido-acetic acid ethyt ester added as ethanol solution (1,2 M of ester) such that reaction temperature maintained at 0°C; reaction mixture 8

= 7.2 Hz, 2H), 1.38 (t, J = 7.2 Hz, 3H).

#### Example 34b

### 3-Bromo-4H-thieno(3,2-b)pyrrole-5-carboxylic acid S

[0205] 3-Bromo-4H-thieno[3,2-b]pymole-5-carboxylic acid ethyl ester was hydrolyzed according to Procedure F (7 agent LOH+45, room temperature overnight, then at 50°C overnight again; aciditied aqueous phase axtracted with ethyl acetatic combined organic phases offer over MgSQ, concentrated; Combined organic phases of first over MgSQ, concentrated; COMS m/e 243,9245.9 ((M-H)\*); H NMR (DMSO-4, 6 12.89 (br.s., 1 H), 12.83 (s., 1 H), 7.56 (s., 1 H), 7.08 (s., 1 H).

#### Example 35

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## 3-Bromo-AH-thiano[3,2-b]pyrrola-5-carboxyfic acid ((1S)-benzyl-3-((3R,4S)-dihydroxypyrrolidin-1-yf)-(2R)-hydroxy-3-oxo-propyf-amide 2

## [0207] 3-Bromo 4H-thieno[3,2-bpyrrole-5-carboxyllc acid and (3S)-amino-1-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-4-phenyl-butan-1-one were coupled according to Procedure B (reaction mixture partitioned between ethyl acetate and water prior to acidic washing). \$

CIMS mo 508.0/510.0 (MH\*); 'H NMR (ÖMSO-4), 8 11.36 (s, 0.5H), 11.31 (s, 0.5H), 7.90 (d, J=8.3 Hz, 1H), 7.46 (s, 0.5H), 7.40 (m, JH, 7.80 (m, JH, 7.40 (m, JH), 4.40 (m

#### Example 36

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# 2-Chloro-4H-thiene[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-3-((3R,4S)-dihydroxypyrolidin-1-yl)-(2R)-hydroxy 3-oxo-propyll-amide

## 2-Chloro-4H-thieno[3,2-b]pyrrole-5-carboxylic acid and (3S)-amino-1-((3R,4S)-dihydroxy-pyrrolidin-1-yl) [0208]

8

(2R)-hydroxy-4-phenyl-butan-1-one were coupled according to Procedure B (reaction mixture partitioned between ethy acetate and water prior to acidic washing).

CINS TWO 464 02466 (MHT); TH NINT (DINSO-4), 6 11.72 (s. 0.5H), 11.67 (s. 0.5H), 7.85 (d. J = 9.1 Hz, 1H), 7.21 (m. 4.1), 7.12 (m. 4.1), 7.13 (m. 7.1), 7.13 2

2

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#### Example 36a

## 2-Chloro-4H-thieno[3,2-b]pyrrole-5-carboxylic acid ethyl ester

- 9] 5-Chloro-thiophene-2-carbaidehyde was annulaised according to Procedure H (aldehyde and azido-acetic acid ester added as ethanol solution (1.2 M of ester) such that reaction temperature maintained at 0-5°C; reaction extractions, combined acrylate organic phases washed with water until aqueous phase was neutral; 0.5 M solution of mixture allowed to warm to room temperature, stirred for 2 h, poured into cold saturated aqueous NH4Cl; after ether crude acrylate heated for 1.5 h).
  - CIMS m/e 228.0/229.9 ((M-H)+); 14 NMR (CDCI3) 8 9.04 (br s, 1H), 7.02 (m, 1H), 6.88 (m, 1H), 4.34 (q, J = 7.2 Hz, 2H), 1.37 (t, J = 7.2Hz, 3H).

#### Example 36b

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### 2-Chloro-4H-thieno[3,2-b]pyrrole-5-carboxylic acid 5

- 2-Chloro-4H-thieno[3,2-b]pyrrole-5-carboxylic acid ethyl ester was hydrolyzed according to Procedure F (50°C 9 h). [0210]
  - CIMS m/e 189.9/201.8 ((M-H)+); 14 NMR (DMSO-4g) & 12.62 (s, 1H), 12.04 (s, 1H), 7.05 (s, 1H), 6.97 (s, 1H).

#### Example 37

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# 2-Chloro-4H-thleno[3,2-b]pyrrole-5-carboxylic acid [(18)-benzyl-2-((3R,4S)-dihydroxypyrrolidin-1-yl)-2-oxo-ethylj-amide

- [021] 2-Chloro-4H-thieno(3,2-bjpyrrole-5-carboxylic acid and (2S)-amino-1-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-3-phenyl-propan-1-one hydrochloride were coupled according to Procodure B (reaction mixture partitioned batween ethyl acetate and water prior to acidic washing).
- CINS me 434 0/436.0 (MH+); <sup>1</sup>H NMR (DMSÖ-4<sub>6</sub>) 5 11.73 (m, 14), 8.57 (d, J = 7.9 Hz, 14), 7.28-7.19 (m, 44), 7.13 (m, 2H), 7.01 (d, J = 2.7 Hz, 1H), 5.00 (d, J = 5.2 Hz, 0.5H), 4.92 (d, J = 5.2 Hz, 0.5H), 4.88 (m, 1H), 4.79 (m, 1H), 4.09 (m, 1H), 3.82 (m, 1.5H), 3.42 (a, 2H), 3.14 (m, 1.5H), 3.01 (m, 1.5H), 3.82 (m, 1.5H), 3.42 (a, 2H), 3.14 (m, 1.5H), 3.01 (m, 1.5H), 3.02 (m, 1.5H), 3.02 (m, 1.5H), 3.02 (m, 1.5H), 3.02 (m, 1.5H), 3.01 (m, 1.5H), 3.01 (m, 1.5H), 3.01 (m, 1.5H), 3.02 (m, 1.5H), 3.02 (m, 1.5H), 3.01 (m, 1 8

#### Ехатріе 38

## 3-Methyl-4H-thleno[3,2-b]pymole-5-carboxylic acid [(15)-benzyt-2-((3R,AS)-dihydroxypymolidin-1-yl)-2-oxo-ethyl amide 33

- [0212] 3-Methyl-4H-thieno[3,2-b]pyrrole-5-carboxyiic acid and (2S)-amino-1-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-3-phenyl-propan-1-one hydrochlorde were coupled according to Procedure B (reaction mixture partitioned between
- ethyl acetale and water prior to acidic washing).
  MS. The A. (Michyl, A. A. (Michyl, H. Mark (MSCO-4<sub>6</sub>), § 11.69 (m, 14), 8.45 (m, 14), 7.28-7.18 (m, 44), 7.12 (m, 24), 8.33 (d, J = 1.0 Hz. 14), 4.83 (d, J = 1.0 Hz. 14), 4.83 (d, J = 2.2 Hz. 0.54), 4.90 (d, J = 5.0 Hz. 0.54), 4.83 (m, 2.4), 4.03-3.22 (m, 2.54), 3.14 (m, 14), 3.03 (m, 1.54), 3.42-3.23 (m, 2.54), 3.14 (m, 14), 3.03-2.88 (m, 2.4), 2.24 (s, 34). \$

#### Example 38e

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# 3-Methyl-4H-thleno[3,2-b]pyrrole-5-carboxylic acid ethyl ester

reaction poured into cold saturated equeous NH $_4$ Cl; after either extractions, acrylate organic phase washed with water uniting queous phase was neutral; seryfate not purified). CIMS rive 207.9 ((M+Hy), 208.9 (MH+); H NMR (CDCl $_4$ ) 8 9.02 (br a, 1H), 7.09 (d, J = 1.9 Hz, 1H), 6.91 (d, J = 1.0 Hz, 1H), 6.35 (quert, J = 7.3 Hz, 1H), 2.32 (d, J = 1.2 Hz, 3H), 1.38 (t, J = 7.2 Hz, 3H). [0213] 4-Methyl-thiophene-2-carbaldehyde (Detty, M. R.; Hays, D. S., Heterocycles, 40: 925-37 (1995)) was annu-lated according to Procedure H (aldehyde and azido-acetic acid ethyl ester addod as ethanol solution (1.1 M of ester); 8

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## 3-Methyl-4H-thleno[3,2-b]pyrrole-5-carboxylic acid

[0214] 3-Methyl-4H-thieno(3,2-b]pyrrole-5-carboxylic acid ethyl ester was hydrolyzed according to Procedure F (50°C 13 h; acidified aqueous phase extracted with ethyl acetate; combined organic phases dried over MgSO4. con-CIMS m/e 179.9 ((M-H)\*), 181.8 (MH\*); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) & 12.45 (br.s., 1H), 11.99 (s, 1H), 7.02 (m, 1H), 6.96 (m, 1H), 2.25 (s, 3H).

#### Example 39

9

# 3-Methyl-4H-thleno(3,2-b)pyrrole-5-carboxylic scid ((1.S)-benzyl-3-((3R,4S)-dihydroxypyrrolldin-1-yl)-(2R)-hydroxy-3-oxo-propyll-smide

[0215] 3-Methyl-4H-thieno[3.2-bjpyrrole-5-carboxylic ecid and (3S)-amino-1-((3R,4S)-clinydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-4-phenyl-butan-1-one-were coupled according to Procedure B (reaction mixture partitioned between ethyl sociate and water prior to acidic washing).

CIMS mo 442.1 ((M+H)"), 444.0 (MH"), "H NMR (DMSO-4<sub>6</sub>), \$ 11.66 (s, 0.5H), 11.62 (s, 0.5H), 7.76 (d, J = 8.9 Hz, 11.77 (d, J = 1.7 Hz, 1H), \$ 158 (d, J = 7.8 Hz, 0.5H), \$ 15.8 (m, J H), \$ 20 (m, J H), 7.21 (m, J H), 7.20 (d, J = 1.7 Hz, 1H), \$ 16.8 (d, J = 7.8 Hz, 0.5H), \$ 16.8 (m, J H), \$ 2.8 (m, J 8

#### Example 40

## 2-Cyano-4H-thiono(3,2-b)pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-cihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-53

[0216] 2-Cyano-4H-thieno[3,2-b]pyrrole-5-carboxylic acid and (2S)-amino-1-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-3-phenyl-propan-1-one hydrochlorde were coupled according to Procedure B (reaction mixture partitioned between 8

ethyl acetate and water prior to acidic washing). CIMS m'e 423.1 ((M-H)\*), 425.1 (MH\*); \*H NMR (DMSO-4g) 8 12.15 (m, 1H), 8.85 (d, J = 8.3 Hz, 1H), 7.79 (m, 1H), 7.29-7.11 (m, 6H), 5.00 (m, 0.5H), 4.93-4.78 (m, 2.5H), 4.04-3.93 (m, 1H), 3.81 (m, 1.5H), 3.43-3.25 (m, 2.5H), 3.15 (m, 1H), 3.03-2.89 (m, 2H).

#### Example 40a

8

## 2-Formyl-4H-thleno[3,2-b]pyrrole-5-carboxylic acid

[0217] 2-Formyl-4H-thieno(3.2-b]pytrole-5-carboxylic acid ethyl ester (see, for example, Gale, W. et al., J. Org. Gene., 22 2150-2155 (1980) was hydrolyzed according to Proceedure (1907 covernight; acidilide aqueous phase extracted with ethyl acetate; combined organic phases dried over MSSOs, concentrated).

CIMS rive 183.8 ((M-H)\*), 195.8 (MH-Y)\* 14 NMR (DMSO-dg) 8 13.38-12.78 (br s, 1H), 12.43 (s, 1H), 9.90 (s, 1H), 7.92 (s, 1H), 7.08 (s, 1H) \$

#### Example 40b

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## 2-Cyano-4H-thieno(3,2-b)pyrrole-5-carboxylic acid

[0218] 2-Formyl-4H-thienq(3,2-b]pymole-5-carboxylic acid was treated with hydroxylamine hydrochloride according to Procedure G. CIMS m/o 190.9 ((M+H)\*\*); \*\*H NMR (DMSO-4<sub>6</sub>) & 13.06 (br s, 1H), 12.45 (s, 1H), 7.84 (s, 1H), 7.09 (s, 1H). 8

#### Example 41

# 2-Cyano-4H-furo[3,2-b]pymole-5-carboxyilc acid [(1S)-benzyl-3-((3R,4S)-dlhydroxypymolidin-1-yl)-(2R)-hydroxy

d reaction time; reaction mixture partitioned between ethyl acetate and water; organic phase washed with 2 N HCI [0219] 2-Cyano-4H-turo(3,2-blpymole-5-carboxylic acid and (3S)-amino-1-((3R,4S)-dihydroxy-pymolidin-1-yl)-(2R)-hydroxy-4-phenyl-butan-1-one were coupled according to Procedure A (1 equiv triathylamine, dimathylformamide; 4 prior to saturated aqueous NaHCO3).

mp 137-140°C; CIMS me 437.1 ([M-H]·), 439.0 (MH·); 'H NMR (DMSO-d<sub>0</sub>) δ 11.70 (m, 1H), 7.89 (d, J = 8.9 Hz, 1H), 7.56 (m, 1H), 5.22 (m, 4H), 7.22 (m, 4H), 4.89 (d, J = 5.2 Hz, 0.5H), 4.83 (d, J = 7.3 Hz, 0.5H), 4.83 (d, J = 3.9 Hz, 0.5H), 4.82 (m, 1H), 4.83 (d, J = 7.3 Hz, 0.5H), 4.83 (m, 2H), 3.81+3.50 (m, 2H), 3.28-2.80 (m, 2H), 3.24 (m, 1H), 4.08-3.89 (m, 2H), 3.28-2.80 (m, 2H), 4.83 (m, 9

#### Example 42

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# 3-Bromo-4H-furo(3,2-b]pyrrole-5-carboxylic acid ((1S)-benzyi-2-((3R,4S)-dihydroxypyrroiidin-1-yl)-2-oxo-athyl-amida

partitioned between eltry acetale and water; organic phase washed with 2 N HCl prior to saturated aqueous NaHCO<sub>3</sub>).

mp 140°C dec.; CIMS m/o 461.9/463.8 (MH\*); <sup>1</sup>H NMR (300 MHz, DMSO-4<sub>6</sub>) 6 11.75 (m, 1H), 8.47 (d, J = 8.6 Hz, 1H), 7.30 (d, J = 0.8 Hz, 1H), 5.03 (d, J = 5.3 Hz, 0.5H), 4.96 (d, J = 5.1 Hz, 0.5H), 4.91 4.83 (m, 2H), 4.13-3.87 (m, 1H), 3.06 (m, 1.5H), 3.48-3.25 (m, 2.5H), 3.18 (m, 1H), 3.06-2.82 (m, 2.5H), 4.13-3.87 (m, 1H), 3.06 (m, 1.5H), 4.13-3.87 (m, 1H), 3.06-2.82 (m, 3.48-3.25 (m, 2.5H), 3.18 (m, 1H), 3.06-2.82 (m, 3.48-3.25 (m, 3.5H), 3.18 (m, 3.5H), 4.13-3.87 (m, 3.5 [0220] 3-Bromo-4H-turo[3,2-bpymole-5-carboxylic acid and (2S)-amino-1-((3R,4S)-dihydroxy-pymolidin-1-yl)-3-phenyl-propan-1-one hydrochloride were coupled according to Procedure A (dimethylformamide; reaction mixture 8

#### Example 42a

23

## 3-Bromo-4H-furo[3,2-b]pyrrole-5-carboxylic acid ethyl ester

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[0221] 4-Bromo-2-furaldehyde was annulated according to Procedure H (aldehyde and azido-acetic acid ethyl ester added as ethanol solution (1 M of ester) to -20 °C ethoxide solution; -20 °C 35 min, -5°C 1.5 h, 5°C 15 min, reaction prograd into color asturated agusous NH,Cl; after either extraction, acrylate organic phase washed with water until aqueous phase was neutrated agusous of crude acrylate heated).

CIMS mio 257 812598 (MH+y; H NIM (30 MH+z, COC<sub>2</sub>) 8 8.81 (for s, 1 H), 7.48 (s, 1 H), 6.79 (d, J = 1.8 Hz, 1 H), 4.35 (d, J = 7.1 Hz, 2 H), 1.36 (t, J = 7.1 Hz, 2 H), 1.36 (t, J = 7.1 Hz, 2 H), 1.36 (t, J = 7.1 Hz, 2 H), 6.79 (t, J = 1.8 Hz, 1 H), 4.35

33

## 3-Bromo-4H-furo[3,2-b]pyrrole-5-carboxylic acid

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[0222] 3-Bromo-4H-furo[3,2-b]pyrrole-5-carboxylic acid ethyl ester was hydrolyzed according to Procedure F (50°C 14 h; additind aqueous phase artracted with eithy acetatic organic phase dred over MgSO<sub>4</sub>, concantrated). CIMS nwe 528 0230.0 ((M-H)<sup>\*</sup>); <sup>1</sup>H NMR (300 MHz, DMSO-4<sub>6</sub>) δ 12.60 (br s, 1H), 12.06 (br s, 1H), 7.96 (s, 1H), 8.77 (d, J= 1.8 Hz, 1H).

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#### Example 43

## 3-Bromo-4H-furo[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-3-((3R,4S)-dihydroxypyrrollidin-1-yl)-(2R)-hydroxy 8

## 3-oxo-propyi]-amide

hydroxy-4-prienyl-butan-1-one were coupled according to Procedure A (1 equiv triethylamine, dimethyliomamide; re-action mixture partitioned between eithyl acetate and water, organic phases washed with Z N HCI prior to eaturated eaction mixture partitioned between eithyl acetate and water, organic phases washed with Z N HCI prior to eaturated action of AHCO<sub>2</sub>), mp 140°C dec; CIMS mv 492.0494 (0.0HH); H NNH (300MH); DNSC-04, B 11.73 (s. 0.5H), 11.68 (s. 0.5H), 788 (d. j. = 0.7 Hz, HH), 7.79 (d. j. = 89. Hz, 1H), 7.27 (m. 4H), 7.17 (m. 1H), 6.18 (s. 1H), 5.18 4.74 (m. 3H), 4.56 4.40 (m. 1H), 4.24 (s. 1H), 4.05-3.94 (m. 1.5H), 3.64-3.11 (m. 4.5H), 3.02-2.85 (m. 2H). [0223] 3-Bromo-4H-furo[3,2-b]pyrrole-5-carboxylic acid and (3S)-amino-1-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-55

#### amole 44

4H-1,7-Dithla-4-aza-cyclopenta[a]pentalene-5-carboxylic acid [(1S)-benzyl-3-((3R,4S)-dlhydroxy-pymolidin-1-y/)-

droxy-3-oxo-propyl]-amide

[0224] 4H-1,7-Dithle 4-eza-cyclopenta[alpentalene-5-carboxylic acid and (3S) amino-1-((3R,4S)-dihydroxy-pyrrolldin-1-yl)/CRIP-hydroxy-4-phenyl-butan-1-one were coupled according to Procedure B [2:1 dichloromethane:dimethyrlommanibar, reaction miturus partitioned between ethyl acetate and water; organic phase washed with 2 N HCI prior to saturated aqueous MAHCO<sub>2</sub>). CIMS mo 484.0 ((M-H)\*), 486.0 (MH\*); <sup>1</sup>H NMR (DMSO-4<sub>0</sub>) 8 12.00 (e, 0.5H), 11.95 (e, 0.5H), 7.83 (m, 1H), 7.55 (dd,

CIMS.mfo.84840 ((M-H)\*), 486.0 ((M+Y); <sup>1</sup>H NMR (DMSO-4<sub>6</sub>), 8 12,00 (s. 0.5H), 11.96 (s. 0.5H), 7.83 (m. 1H), 7.55 (dd. 1-0.8, 6.2 Hz, 1H), 7.35 (dd. 1-1.2, 6.2 Hz, 1H), 7.25 (m. 4H), 7.12 (m. 2H), 5.07 (dJ. 1-7.3 Hz, 0.5H), 4.96 (m. 1H), 4.90 (dJ. 1-5.0 Hz, 0.5H), 4.81 (dJ. 1-7.5 Hz, 0.5H), 4.78 (dJ. 1-4.2 Hz, 0.5H), 4.44 (m. 1H), 4.20 (m. 1H), 4.06-3.8 (m. 1.5H), 3.57 (m. 1H), 3.40 (m. 0.5H), 3.26 (m. 1.5H), 3.17-3.07 (m. 1.5H), 2.87-2.84 (m. 2H).

#### Example 44a

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# 4H-1,7-Dithia-4-aza-cyclopenta[a]pentalene-5-carboxylic acid ethyl ester

[0225] Thleno[2,9-bjthlophene-2-carbaldehyde (Dopper, J. H. et al., J. Am. Chem. Soc., <u>95</u>; 3692-8 (1973)) was annulated according to Procedure H (atchtyde and actio-sectic acid ethyl ester acided as ethanol solution (1 M of estar) to -20°C coltavide solution; 2:0°C 30 min., 2:0°C to room temperature over 2:5 h; reaction poured into cold saturated aqueous NH<sub>2</sub>(); after ether extraction, acrylatio organic phase washed with water until aqueous phase was neutral; 0:35 M solution of crude acrylate heated).

Elementa, v.33 m solution in choos acy ynaer recept, y B 8.48 (br s., 141), 7.35 (d., J = 5.3 Hz, 1H), 7.29 (d., J = 5.3 Hz, 1H), 7.29 (d., J = 5.3 Hz, 1H), 7.10 (d., J = 2.0 Hz, 1H), 7.14 (d., J = 2.0 Hz, 1H), 7.14 (d., J = 2.0 Hz, 1H), 7.15 (d., J = 7.1 Hz, 2H), 1.39 (t., J = 7.1 Hz, 3H)

#### Example 44b

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# 4H-1,7-Dithia-4-aza-cyclopenta[a]pentalene-5-carboxyfic acid

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[0226] 4H-1,7-Dithia-4-eza-cyclopenta[a]pentalene-5-carboxylic acid elnyl ester was hydrolyzed according to Procedure F(59°C II II), Codius nve 222.0 ((M-H)); 'H NMR (DMSO-4<sub>6</sub>) 5 12.51 (s, 1H), 12.32 (s, 1H), 7.59 (d, J = 5.3 Hz, 1H), 7.38 (d, J = 5.3 Hz, 1H), 7.65 (d, J = 1.9 Hz, 1H).

#### Example 45

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# 4H-1,7-Dithla-4-aza-cyclopenta(a)pentalene-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-y/)-

# 2-oxo-ethyll-emide

[0227] 4H-1,7-Dithis 4-aza-cyclopentale)pentalene-5-carboxyfic acid and (2S)-amino-1-((3R,4S)-ditydroxy-pytrolidin-1-yi)3-pinoty-propant-one hydrochloride were coupled according to Procedure B (1:1 dichibiormethane-dimethyfumramide; reaction mixture partitioned between eithyl acetate and water, organic phase washed with 2 N HCl prior to saturated aqueous NeHCO<sub>2</sub>).

CMS me 454.0 ((M·H)\*), 458.0 (MH\*); \*H NMR (DMSO-4<sub>6</sub>), 612.03 (m, 1H), 8.53 (d, J = 8.1 Hz, 1H), 7.55 (dd, J = 0.8, Ez.Hz, 1H), 7.34 (dd, J = 2.7, 5.2 Hz, 1H), 7.29+7.18 (m, 5H), 7.12 (m, 1H), 4.99 (d, J = 5.2 Hz, 0.5H), 4.91 (d, J = 5.0 Hz, 0.5H), 4.94 (m, 2H), 3.98 (m, 1H), 3.83 (m, 2H), 3.41-3.29 (m, 3H), 3.13 (m, 1H), 2.95 (m, 2H),

#### Example 46

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2-Chloro-3-methyl-4H-thiena(3,2-b)pyrrole-5-cerboxyic.ecid ((1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxoethyl-emide [0228] 2-Chloro-3-mathyl-4H-thieno(3,2-b]pyrrole-5-carboxylic acid and (2S)-amino-1-((3R,4S)-dihydroxy-pyrrolidin-1-th)-3-phenyi-propan-1-one hydrochloride were coupled according to Procedure B (1:1 dichloromethan-cidmethyrloromanide; 2 of reaction time; reaction mixture concentrated to remove dichloromethane; partitioned between eithyl accitate and water, organic phase washed with 2 N HCl prior to saturated aqueous NaHCO<sub>2</sub>, mp 139-141°C; CIMS mle 448.1/450.1 (MH+); 1H NMR (DMSO-4g) 8 11.95 (m, 1H), 8.54 (d, J = 7.9 Hz, 1H), 7.29-7.18 (m, 4H), 7.13 (m, 2H),

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4.98 (d, J = 5.2 Hz, 0.5H), 4.90 (d, J = 4.6 Hz, 0.5H), 4.83 (m, 2H), 4.02.3.92 (m, 1H), 3.82 (m, 1.5H), 3.41.3.22 (m, 2.5H), 3.14 (m, 1H), 3.01.2.90 (m, 2H), 2.20 (d, J = 2.5 Hz, 3H).

#### Evaluate 108

## 5-Chloro-4-methyl-thiophene-2-carbaidehyde

Rablohn, e.d. p. 831), to a BCC pale yelbw solution of Schenz-Snathesis Coll. Vol 4, Wiley, NowYork, 1963, N. Apalohn, e.d. p. 831), to a BCC pale yelbw solution of Schoho-Snathythiophone (Crast. L. B., H. U.S.). Pationt 3290291. Example 2, 70 g, 0.53 mol) in dimentifytiomamide (48.3 g, 0.66 mol) was added phosphorus oxychionida (101.5 g, 0.66 mol) was added phosphorus oxychionida (101.5 g, 0.66 mol) was added phosphorus oxychionida (101.5 g, 0.66 mol) was added phosphorus oxychionida similared a 90°C for 3 h and poured slowly in water (500 m), et 90°C. The resultain mixture was assem distilled and similared any oxychionida was recoystallized from hexane (150 m) at -50°C. The crude product (8.6 g) was dissolved in hoxane (100 m) and the insoluble material was filtered. The filtrate was diluted with bexane (50 m), stritted with Norling (2), and concentrated. The product was pullid by rocycstallization from hoxane (50 m) at -40°C and oxisined as white crystals (7.5 g, 13%). The remaining distillate from the steam distillation was extracted with chordom (2 x 550 m) and the white crystals dissolved in chloroform (1.5 f). The croticule was dissolved in hoxane (50 m) the distillation was a white crystals (30.3) for 15 mill, and concentrated. The residue was dissolved in hoxane (30 m), the insoluble material was filtered, the filterial was a filtered, the filterial was filtered.

20 insoluble material was filtered, the filtrate was stirred at ·15 °C for 10 min, and the resultant precip The title product was obtained as pale yellow crystals (48.6 g. 83%); mp 39-40°C.

#### Example 46b

# 25 2-Chloro-3-methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid ethyl ester

[0230] 5-Chloro-4-methyl-thlophene-2-carbaldehyde was annulated according to Procedure H (aldehyde and azidoaccilic acid ethyl ester was added as ethanol solution (1 M of ester) to -20°C ethoxide solution; allow to warm to 10°C over 2 h, 10°C 2 h; reaction poured into cold saturated aqueous NH<sub>4</sub>Ci; after either extraction, acrylate organic phase washed with water until aqueous phase was neutral; solution of crude acrylate addod to refluxing xylenes over 5 min and then heated at reflux).

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CIMS n/ve 243.8/245.9 (MH\*); 14 NIMR (CDCc<sub>ts</sub>) 89.25 (br.s., 1H), 7.02 (d. J = 1.9 Hz, 1H), 4.36 (q. J = 7.1 Hz, 2H), 2.28 (s. 3H), 1.38 (t. J = 7.1 Hz, 3H).

#### Example 46c

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## 2-Chloro-3-methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid

[0231] 2-Chloro-3-methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid ethyl ester was hydrotyzed according to Proce-40 dure F (50 °C 14 h).

CIMS m'e 213.8215.8 ((M·H)·); ¹H NMR (DMSO-Œ) 8 12.81 (br s, 1H), 12.25 (s, 1H), 6.96 (dd, J = 0.5, 2.0 Hz, 1H), 2.23 (s, 1H).

#### Example 47

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## 2-Chloro-3-mothyl-4H-thlono[3,2-b]pyrnole-5-carboxylic acid [(1.5)-benzyl-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)hydroxy-3-oxo-propyll-amide

[0332] 2-Chloro-3-mathy-4H-thleno[3.2-bjpyrrole-5-carboxylic acid and (35)-amino-1-(16R-45)-dihydroxy-syrrolld30 in-1-yh)-(2R)-hydroxy-4-phrayh-bulan-1-ton ware coupled according to Procedure B (4.5 dichloromethaned/imethyformanide, 2 d reaction time; reaction mixtus concentrated to remove dichloromethane; partitioned between eithy
accitate and water; organic phase washed with 2 N HCI pring is saturated equeous NHCQ).

exetate and water; organic phase washed with 2 N HCl prior to saturated aqueous NaHCO<sub>2</sub>).

rm 150-153°C; CIMS me 478.1/480. (MH+); H NMR (DMSO-4<sub>6</sub>) 5 11.91 (8, 0.5H), 11.86 (8, 0.5H), 7.82 (d, J = 8.7, 1H), 7.22 (m, 4H), 7.11 (m, 1H), 7.01 (m, 1H), 5.07 (d, J = 6.8 Hz, 0.6H), 4.85 (m, 1H), 4.90 (d, J = 5.0 Hz, 0.5H), 4.82 (d, J = 6.8 Hz, 0.5H), 4.82 (m, 1H), 4.20 (m, 1H), 4.08 (m, 1.5H), 3.58 (m, 1H), 3.40 (m, 0.5H), 2.95-2.82 (m, 2H), 4.09 (m, 0.5H), 2.95 (m, 1H), 3.40 (m, 0.5H), 2.95 (m, 2H).

#### Example 48

# 2-Methylsulfanyl-4H-thieno[3,2-b]pyrrole-5-carboxyllc acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo

1-yt)-3-phenyl-propan-1-one hydrochloride were coupled according to Procedure B (1:1 dichloromethane:dimethylfor-mamide; reaction mixture concentrated to remove dichloromethane, partitioned between ethyl acetale and water, or-[0233] 2-Methylsulfanyt-4H-thleno[3,2-b]pyrroko-5-carboxylic acid and (2S)-amino-1-((3R,4S)-dihydroxy-pyrrolidin ganic phase washed with 2 N HCI prior to saturated aqueous NaHCO<sub>3</sub>).

mp 104-110°C; 444.0 ((M-H)°, 445.9 (MH°); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)) 5 11.51 (m, 1H), 6.52 (d, J = 8.6 Hz, 1H), 7.28-7.12 (m, 6H), 6.97 (d, J = 3.9 Hz, 1H), 4.98 (d, J = 5.1 Hz, 0.5H), 4.91 (d, J = 5.1 Hz, 0.5H), 4.83 (m, 2H), 4.08-3.94 (m, 1H), 3.80 (m, 2H), 3.43-3.24 (m, 2H), 3.14 (m, 1H), 3.02-2.87 (m, 2H), 2.46 (s, 3H).

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# 2-Methylsulfanyl-4H-thleno[3,2-b]pyrrole-5-carboxylic acid ethyl ester

4 h; reaction poured into cold saturated aqueous NH<sub>4</sub>Ci; after ether extraction, acrylate organic phase washed with acetic acid ethyl ester added as ethanol solution (1 M of ester) to -20°C ethoxide solution; allow to warm to 10°C over 5-Methylsulfanyl-thiophene-2-carbaldehyde was annulated according to Procedure H (aldehyde and azido water until aqueous phase was neutral; crude acrylate solution heated at reflux for 2 h, allowed to cool to room ternperature, stirred overnight). [0234] 8

CIMS m'e 240.0 ([M.H!"), 242.0 (MH"); 'H NMR (CDC<sub>3</sub>) 8 9.05 (br s, 1H), 7.04 (m, 1H), 8.97 (s, 1H), 4.35 (q, J=7.1 Hz, 2H), 2.53 (s, 3H), 1.37 (t, J= 7.1 Hz, 3H).

#### Example 48b

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## 2-Methylsuffanyl-4H-thleno[3,2-b]pyrrole-5-carboxylic acld

[0235] 2-Methylsullanyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid ethyi ester was hydrolyzed according to Procedure 8

CIMS m'e 211.9 ((M.H.)); 'H NMR (DMSO-4<sub>6</sub>) 6 12.56 (s, 1H), 11.90 (s, 1H), 6.97 (s, 1H), 6.94 (s, 1H), 2.47 (s, 1H) [**02**36] A preferred subgroup of formula (IV) compounds are those compounds selected from the group consisting of:

(±)-2 bromo-4H furo[3,2-b]pyrrole-5-carboxylic acid-[1-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-2-chloro-6H-thleno[2,3-b]pyrrole-5-carboxylic a

2-bromo-4H-thieno[3,2, b]pyrrole-5-carboxylic acid-{(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1

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acid-{(1S)-benzyi-2-(1,1dioxo-1-thlazolidin-3-yi)-2-oxo-ethyl]--chloro-6H-thieno[2,3-b]pyrrole-5-carboxylic acid-{(1S)-benzyl-2-morpholin-4-yl-2-oxo-ethyl]-amlde; 2-chloro-6H-thleno[2,3-b]pyrrole-5-carboxyilc 2-chioro-4H-funo[3,2-b]pyrroie-5-carboxylic acld-[(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolldln-1-yl)-2-oxo-ethyl]-

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2-chloro-4H-furo[3,2-b]pyrrole-5-carboxyiic acid-[(1S)-benzyl-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)hydroxy-3-oxo-propyf]-amide;

2-chloro-4H-thieno[3,2-b]pyrrole-5-carboxylic ethylj-amide; and

acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxoethyl)-amide; the stereoisomers and prodrugs thereof, and the pharmaceutically acceptable salts of the com-3-methyl-4H-thieno(3,2-b)pyrrole-5-carboxylic pounds, stereolsomers and prodrugs. 8

[0237] Another aspect of the invention provides methods of treating prophylactically an individual in whom Type 2 diabetes mellitus has not yet presented, but in whom there is an increased risk of developing such condition, which methods comprise administering to an individual in need thereof effective amounts of a glycogen phosphorylase inhibitor and a non-glycogen phosphorylase Inhibiting anti-diabetic agent, or a glycogen phosphorylase inhibitor and an antl-obesity agent, preferably in the form of a pharmaceutical composition. 8

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generally preferred glycogen phosphorylase inhibitors may comprise, for example, the com salts of the compounds, stereolsomers, and prodrugs depicted hereinabove.

synthase kinase inhibitors; and the like. Other non-glycogen phosphorylase inhibiting anti-diabetic agents, inctuding Generally preferred non-glycogen phosphorylase inhibiting anti-diabetic agents may comprise, for axample O-chiroinositol; insulin and insulin analogs; GLP-1 (7-37)(insulinotropin) and GLP-1 (7-36)-NH<sub>2</sub>; α-glucosidasa inhib zolines; insulin secretagogues; aldose reductase inhibitors; fatty acid oxidation inhibitors; β-agonists; phosphodieste rase inhibitors; lipid-lowering agents; vanadate and vanadium complexes; amylin antagonists; glucagon antagonists growth hormone secretagogues; gluconeogenesis inhibitors; somatostatin analogs; antilipolytic agents; lipoxygenase inhbitors; Insulin signaling agonists; insulin mimetics; PTP1B inhibitors; insulin degrading enzyme inhibitors; glycoger the preferred agents set forth hereinbelow, are well known, or will be readily apparent in light of the instant disclosure kors; glitazones and/or insulin senskizers; sulfonylureas and analogs thereof; biguanides; ຜ<sub>2</sub>-antagonists and imida to one of ordinary skill in the art. 9

Preferred gluconeogenesis inhibitors useful in the methods of the invention may comprise, for example, glucose-Pephosphalase inhibitors, or GR 3034. Preferred entillipotytic agants useful in the methods of the invention may com-prise, for example, nicotinic acid, acipimox, and WAG 994. Preferred amylin antagonists useful in the methods of the invention may comprise, for example, premithinds and AC-137. Preferred glucagon antagonists useful in the methods of the invention may comprise, for example, BAY 27-9955. Preferred Bloxygenese Inhibitors useful in the methods of nide. Preferred biguanides useful in the methods of the invention may comprise, for example, metformin, phenformin, and buformin. Preferred o<sub>2</sub>-antagonists and traidazolines useful in the methods of the Invention may comprise, for aldose reductase Inhibitors useful in the methods of the invention may comprise, for example, epairestat, sorbinil, tofrestat, zenarestat, and zopotrestat. Proferred fatty acid oxidation inhibitors useful in the methods of the invention may comprise, for example, clomoxir and elomoxir. Preferred β-agonists useful in the methods of the Invention may comprise, for example, BRL-35135, BRL-37344, TAK-667, AZ 40140, and CL 316,243. Preferred phosphodiestenss the invention may comprise, for example, masoprocol. Preferred insulin signaling agonists useful in the methods of [0240] Preferred forms of insulin useful in the methods of the invention may comprise, for example, inhaled insulin, or insulin analogs, for example, LysPro Insulin. Preferred α-giucosidase inhibitors useful in the methods of the invention may comprise those agents such as acarbose, voglibose, miglitol, emiglitate, camiglibose, MDL-25637, and MDL-73,945. Preferred giltazones and/or insulin sensitizers useful in the methods of the invention may comprise, for example, ciglitazone, pioglitazone, englitazone, troglitazone, darglitazone, rosiglitazone, ЛТ-501, MCC-555, and MX 6054. Proferred sulfonylureas and analogs thereof useful in the methods of the Invention may comprise, for example, chlorpropamide, glibenclamide, tofbutamide, tolazamide, acetohexamide, glipizide, glimepiride, repaglinide, and meglitiexample, midaglizole, isaglidole, deniglidole, idazoxan, elanoxan, and flupanoxan. Preferred insulin secretagogues use-ful in the methods of the Invention may comprise, for example, linoglirde, A-4166, exendin-4, and BTS-67582. Preferred inhibitors useful in the methods of the invention may comprise, for example, L-386,398. Preferred lipid-towering agents useful in the methods of the Invention may comprise, for example, benfluorex. Preferred vanadate and vanadium complexes useful in the methods of the Invention may comprise, for example, neglivan and peroxovandium complexes. the invention may comprise, for example, L-783281. 2 8 S 8 33

trophic factors (such as Axokine), or human agouti-related protein (referred to hereinatter as AGAP) antagonias. Other anti-obesity agents, including the preferred agents set forth hereinbelow, are well known, or will be readily apparent in agents (such as dextentfuramine or fenfuramine), dopamine agonists (such as bromocriptine), melanocyte-stimulating hormone rocoptor agonists or mimetics, melanocyte-stimulating hormone analogs, melanin concentrating hormone protein-B secretion/microsomal trighyceride transfer protein (apo-B/MTP) inhibitors, MCR-4 agonists, cholecystokinin-A (CCK-A) agonists, monoamine reuptake inhibitors (such as sibutramine), sympathiomimetic agents, serotoninergic antagonists, cannabinold receptor antagonists, the OB protein (leptin), a leptin analog, galanin antagonists, lipase inhibitors (such as orlistat), anorectic agents, for example, bombesin agonists, Neuropeptide-Y antagonists, thyromi metic agents, dehydroepiandrosterones or analogs thereof, glucocorticold receptor agonists or antagonists, orexin receptor antagonists, urocortin binding protein antagonists, glucagon-like peptide-1 receptor agonists, cillary neuro [0241] Generally preferred anti-obesity agents may comprise, for example, β-adrenergic receptor agonists, apolipo light of the instant disclosure, to one of ordinary skill in the art.

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closure of which is hereby incorporated by reference. Especially preferred β-adrenergic receptor agonists disclosed therein are selected from the group consisting of (4-[2-(2-(6-aminopyridin-3-yil-2-(R)-rydroxyethylamino)ethoxyjphe-nyllacetic acid. (4-[2-(2-f6-aminopyridin-3-yil-2-(R)-rydroxylphenylphenylpenzoic acid. (4-[2-(2-f6-aminopyridin-3-yil-2-(R)-rydroxyphylamino)ethoxyjphenylphony [0242] Particularly preferred anti-obesity agents useful in the practice of this invention comprise β-adrenergic recepto agonists, sibutramine, orlistat, fenfluramine, dexfenfluramine, bromocriptine, phentermine, ephedrine, feptin, phenyl propanolamine, and pseudoephedrine. Particularly preferred β-adrenergic receptor agonists include those substituted aminopyridinas disclosed in commonly assigned PCT international Application Publication No. WO 96/35671, the dis-

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droxyethylamino)ethoxy]phenoxy]acetic acid.

(1044) The desage of the glycogen phosphorylase inhibitor to be administered in accordance with the methods of the invention will generally be dependent upon a number of flactors including the health of the subject being treated, the axidant of treatment desages are desired. In general, glycogen phosphorylase inhibitors have been reported with representative desages regress being most about 50.08 to about 50 mg/kg body weight of the individual per day, and preferable desages range from about 0.01 to about 55 mg/kg body weight of the individual per day, and preferable about 15 mg/kg body weight of the individual per day, and in a general desages range from about 10.01 to about 15 mg/kg body weight of the individual per day, and the general desages mange the general desages are applied to the proposition of the individual per day, the intended route of edminimation and the line.

[0244] The dosage of the non-glycogen phosphoryase inhibiting anti-diabetic agent will also be generally dependent upon a number of lectors including the health of the subject being treated, the extent of treatment desired, the nature and third of concurrent therapy, if any, and the frequency of treatment and the neutral post desired, in general, the dosage range of the non-glycogen phosphorylase inhibiting anti-diabetic agent is generally from about 0.001 to about 50 mg/kg body weight of the individual por day, preferably from about 0.01 to about 20 mg/kg body weight of the individual por day, administered as a single or divided doses. However, some variability in the general deseger range may be required depending upon the age and weight of the subject being treated, the intended route of administration, the perticular non-glycogen phosphorylase inhibiting anti-diabetic agent being administered, and the like

the particular non-ghoogen phosphorylase inhibiting anti-diabetic agont being administered, and the like.

[0245] The docaged of the anti-obesity agent will also be generally dependent upon a number of factors including the health of this subject being treated, the actent of treatment desired, the nature and kind of concurrent therapy, if any, and the frequency of treatment and the reduce of treatment desired, the nature and kind of concurrent therapy, if any, and the frequency of treatment and the nature of the effect desired. In general, the dosage range of the anti-obesity agent its generally in the nature got from about 100 mg/kg body weight of the individual per day, administrated as a single or divided dosas. However, some variability in the general dosage range may be required depending upon the age and weight of the subject being treated, the infended route of administration, the particular anti-obesity agent being administered, and lie.

(0246) According to the methods of the invention, a glycogen phosphorylasse inhibitor, a stereoisomer or prodrug thereof, or palameta-eucles becapible sate of the inhibitor, stereoisomer, or prodrug thereof, or palameta-eucles or prodrug intensor, or prodrug, and sensolsomer, or prodrug, and a non-glycogen phosphorylasse inhibiting anti-diabetic agent or anti-obosity agent is administered to the subject in need of treatment thereof, preferrably in the form of a pharmaceutically acceptable sat of the inhibitor, stereoisomer or prodrug tereof, or the pharmaceutically acceptable sat of the inhibitor, stereoisomer or prodrug tereof, or the pharmaceutically acceptable sat of the inhibitor, stereoisomer, or prodrug thereof, or the pharmaceutically acceptable sat of the inhibitor, attereoisomer or prodrug thereof, or the pharmaceutical composition. The glycogen phosphorylase inhibiting anti-diabotic agent or anti-obosity agent may be administrated either separately or in the pharmaceutical composition composition composition composition or prodrug that such administration be oral. However, if the subject boing treated is unable to availor, or oral administration is otherwise impaired or undesirable, parainterial or transdomental administration and enhancement entendential appropriate.

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(0248) According to the methods of the invention, the glycogen phosphorylase inhibitor, a stereoisomer, or prodrug thereod, or a pharmaceutically acceptable sait of the inhibitor, stereoisomer, or prodrug; or the the glycogen phosphorylase inhibitor, a stereoisomer, or prodrug, and the control of the phosphorylase inhibitor, as tereoisomer, or prodrug, and the non-glycogen phosphorylase inhibiting anti-diabetic agent or enti-obesity agont is preferably administrated in the form of a pharmaceutically acceptable carrier, which, or

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diluent. Accordingly, the glycogen phosphorylase inhibitor, a stereoisomer, or prodrug thereof, or a pharmaceutically acceptable said of the inhibitor, atlenediscent, or prodrug, or the line glycogen phosphorylase inhibitor, a talereoisomer, or prodrug thereof, or a pharmaceutically acceptable sail of the inhibitor, stereoisomer, or prodrug, and the non-glycogen phosphorylase inhibiting anti-diabetic agent or anti-obesily agent can be administered separately or together in any conventional oral, parenteral, or transdemial dosage form.

(10249) Sultable pharmaceutically acceptable carriers include inert solid filters or diluents and sterile aqueous or organic buildness. According to the methods of the invention, the glycogen phosphorytase inhibitor, as attendisonner, or producy thereof, or a pharmaceutically acceptable sail of the inhibitor, sterodisonner, or producy grant acceptable sail of the inhibitor, sterodisonner, or producy present in some, or producy and the non-glycogen phosphorylase inhibiting anti-disbetic again or anti-obsety agent will be present in such pharmaceutical compositions in amounts sufficient to provide the destred dosage amount in the ranges described breinabove. Thus, for oral administration, the compounds can be combined with a suitable soil or liquid carrier, vehicle or diluent to form capsules, tablets, pills, powders, syrups, solutions, susponsitions and the tike. The pharmaceutical compositions may contain, if desired, additional components such as flavorents, sweeteners, excipi-

[0250] The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, com starch or galatin; exciplents such as dicatclum phosphate; a disintegrating agent such as aucrose, leades, or sacrohing or adjints acid, a lubricant such as magnesium stearatin, as weetening agent such as aucrose, leades, or sacchaning or adjuvanta including coloring agents, preservants, and antioxidants. When a doceage until form is a capsulo, it may contain, in addition to materials of the above type, a figuid carrier such as a letty oil. Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shelled, sugar, or both, A syrup or eliftr may contain, in addition to the active ingolatin, sucrose as a sweetening agent, methyl or propylperabens as preservatives, a dy earl a flavoring such as charry or orange flavor.

[0251] The pharmaceutical compositions of the invention may also be administrated parenterally. For parenteral ad-

[0251] The phermaceutical compositions of the invention may also be administered parenterally. For parenteral administration, the phermaceutical compositions can be completed with serial equeues to organic mediate lorem injectable solutions or suspensions. Solutions or auspensions. Solutions or auspensions can be propared in water sulfably mixed with a surfactant such as hydroxypropy/cellulose. Dispersions can also be prepared in seasme or peasure of la chanoi, wears, polyoff less, giybcarol, propylate giybcy. In digital ophishylate giybcy, but this per individual mixtures thereot, vegetable oils, M-nothyl glucarnins, polyvinylypricalione, and mixtures thereot in oils as well as aqueous solutions of an water-soluble pharmaceutically acceptable eatis of the compounds or prodrugs of the compounds. Under ordinary conditions of present the growth of mixtures. The injectable solutions propared in this anner can have be administered intraspersioneally, subcultaneously, of inframusecularly, with intermusecular administration being the preferrod parenteral route in humans. Solutions propared of inframusecularly, with intermusecular administration being the preferrod parenteral route in humans. Solutions propared

for intravenous administration are preferably rendered isotonic prior to usage
[0252] The phermacoudised forms suitable for hisotrable use include sterile aqueous solutions or disposabos and sterile preparation of isotrable solutions of disposabon. In all cases, however, the form must be sterile and must be full of the actent that facile syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against contamination by microorganisms such as bacteria and fungition. The ghycogen phosphoryless inhibitor, a sterolsomer, or producy thereof, or a pharmaceutically acceptable.

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[0253] The glycogen phosphorylase inhibitor, a stereolsomer, or prodrug thereof, or a pharmaceutically acceptable and the inhibitor, stereoisomer, or prodrug, or the glycogen phosphorylase inhibitor, as teareoisomer, or prodrug, or the glycogen phosphorylase inhibitor, as teareoisomer, or prodrug, thereoisomer, or prodrug, and the non-glycogen phosphorylase inhibitor, as teareoisomer, or prodrug, and the non-glycogen phosphorylase inhibitor and an inhibiting anti-diabetic agent or anti-obestly agent may also be encapsulated in liposeams to permit intravenous administration thereoi. The phosphorylase and the inhibitor to use in this timention may include lipit vasicles and compress puritables, ingly vasicles, and so character antillamellar vasicles, everse phase evaporation vasicles, large mutillamellar vasicles, and the like, wherein the lipid vasicles are formed by one or more phospholipids such as phospholidy-choline, phospholiacid sold, and the like, in addition, the vasicles may also comprise a steroicomponent such as phosphory.

[0254] The pharmaceutical compositions may also be administered transdemnelly. Suitable formulations for transderormal application include an amount of the glycogen phosphoryase inhibitor, a stereolosmor, or practing therefore, or a
pharmaceutically acceptable sat of the inhibitor, stereolosmer, or prodrug, or the glycogen phosphorylase hibblior, a
stereolosmer, or prodrug thereol, or a pharmaceutically acceptable sat of the inhibitor, stereolosmer, or prodrug thereol, or a pharmaceutically acceptable sat of the inhibitor, stereolosmer prodrug, and the
monthydrogen phosphorylase inhibiting anti-distable agent or anti-obesity agent with a suitable transdermal carrier.
Preferred transdermal carriers include absorbable pharmacologically acceptable solvents to promote and assist passago through the skin of the subject being treated. Characteristically, transdermal devices comprise the form of a
bandage heving a backing member, a reservoir containing the compound, optionally with carriers, optionally a ratecontrolling barrier to deliver the compound to the skin of the subject being treated at a controlled and predelemined
rate over a prolinged period of time, and means to scoule the device to the skin of the subject being treated at the compound.

and one approximate period of this and means to secure the centre to the soul of the soulest being treated. (V255] Methods of preparing the various pharmacoutical compositions with a desired amount of an active ingredient

are known, or will be apparent in light of the instant disclosure, to one of ordinary skill in the art. See, for example, Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA, 18th Edition, (1990).

but in whom there is an increased risk of developing such condition, may be demonstrated according to the following non-glycogen phosphorylase inhibiting anti-diabetic agent, or a combination of a glycogen phosphorylase inhibitor and [0256] The ability of a glycogen phosphorylase inhibitor, a combination of a glycogen phosphorylase inhibitor and e an anti-obesity agent, to treat prophylactically an individual in whom Type 2 diabetes melitius has not yet presented

non-glyzogen phosphorylase inhibiling anti-diabelic agent, or a combination of a glyzogen phosphorylase inhibitor and an anti-obestry agent for the ability to prevent or delay the onset of diabetes in the prone obese Zucker diabetic latry The experimetal protocol described by Sreenan, et al., Am. J. Physiol., 271, E742-747 (1996), may be employed to evaluate the glycogen phosphorylase inhibitor, a combination of a glycogen phosphorylase inhibitor and a rat (Charles River Labs, Wilmington, MA and Genetic Models Inc.; Indianapolis, IN), or for the delay or prevention of

tolerance test period by the treated group compared to the untreated group also indicates that the glycogen phosphorylasse inhibitor and the non-glycogen phosphorylasse inhibiting anti-diabetic agent, or the combination of the glycogen phosphorylase inhibitor and the anti-obesity agent deleyed or glycogan phosphorylasa inhibitor and the non-glycogan phosphorylasa inhibiting anti-diabetic agant, or the combination of the glycogan phosphorylase inhibitor and the anti-obesity agent. The animals can also be administered a glucose tolerance test after the six week treatment period. A reduction in serum glucose or insulin levels during the glucose the onset of insulin resistance or impaired glucose toleration in the prone obese Zucker fatty rat. [0258] Rats six weeks of age may be initiated on a daily regimen of treatment employing a glycogen phosphorylase Inhibitor, a combination of a glycogen phosphorylase inhibitor and a non-glycogen phosphorylase inhibiting anti-diabetic egent, or a combination of a glycogen phosphorylase inhibitor and an anti-obesity agent (p.o. by gavage or in the chrow), while being maintained on a standard rotent delir (Purins 5000 W. F. Febra & Son, Inc.). Abund Brook, NJ. After six weeks, the miss are fasted overright, and blood samples are taken for delamination of serum glucose, insulin, ritghyceride, and free fastly soid concentrations. The results for the treated rate are compared against the untreated rate, and/or free fatty acid levels in the treated group compared to the untreated group indicates delay or prevention of the onset of diabetes or insulin resistance attributable to the glycogen phosphorylase inhibitor, the combination of the and also against the lean littermates, which are considered normal. A reduction in serum glucose, insulin, triglyceride

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[0259] According to the methods described by Thomas, et al., Blochem. Pharm., 56, 1145-1150 (1998), the glycogen phosphorylase inhibitor and a non-glycogen phosphorylase inhibitor and a non-glycogen phosphorylase inhibiting anti-diabetic agent, or a combination of a glycogen phosphorylase inhibitor and an anti-obesity agent can also be testod for delay or prevention of the onset of insulin resistance in dexamethasone-induced hyperglycemic and insulin prevented the onset of diabetes, insulin resistance, and/or impaired glucose tolerance. resistant mice.

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glucose or insulin levels during the glucose tolerance test by the glycogen phosphorylase inhibitor, the combination of the glycogen phosphorylase inhibiting anti-diabetic agent, or the com-[0260] C57BL6 (++) mice (Jackson Laboratory, Bar Harbor, ME) 15 weeks of age may be treated with dexametha-sone at 2.5 mg/kg/day plus the glycogen phosphorylase inhibitor, the combination of the glycogen phosphorylase inhibitor and the non-glycogen phosphorylase inhibiting anti-diabetic agent, or the combination of the glycogen phosphoryiase inhibitor and the anti-obesity agent (p.o. by gavage) or vehicle (untreated) for ten days. At the end of the ten-day period, blood samples are taken for plasma glucose and insulin detamtination in the fed state. The antmats are fasted for 12 hr, and subjected to an insulin tolerance test, comprising blood sampling at 10, 20, and 40 min. after i.p. administration of 0.5 U/kg insulin, for cakulation of plasma glucose disappearance. Atternatively, a glucose tolerance test may be administered to the fasted animals after the ten-day treatment period. A reduction in plasme glucose or insulin tevels in the fed state, a greater plasma glucose disappearance during the insulin tolerance test, and/or lower bination of the glycogen phosphorylase inhibitor and the anti-obesity agent pius dexamethasone-treated group compared to the dexamethasone control group indicates that the glycogen phosphorylase inhibitor, the combination of the glycogen phosphorylase inhibitor and the non-glycogen phosphorylase inhibiting anti-diabetic agent, or the combination of the ghycogen phosphorylase inhibitor and the anti-obesity agent prevented or delayed the onset of insulin resistance. ŝ Ş 8

[0561] Further, according to the method described by Davidson, et al., Am. J. Physiol., 264, E18-23, (1993), the agreement property less inhibitor, a combination of a glycogen phosphoryaes inhibitor and a non-dylocogen phosphoryaes inhibitor and a non-dylocogen phosphoryaes inhibitor and an enti-obesity agent ryless inhabiting anti-disposite agent, or a combination of a glycogen phosphorylase inhibitor and an enti-obesity agent may also be tested for the ability to delay or prevent the onset of insulin resistance induced by a cateforta delt treatment hyperglycemia, and impaired glucose tolerance by the dexamethasone treatment. 2

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the glucose tolerance test, - and/or reduced weight gain or obesity (adpose depot weight) by the glycogen phosphor-ylese inhiblior, the combination of the glycogen phosphorylese inhibitor and the non-glycogen phosphorylese inhibiting the combination of the glycogen phosphoryase inhibitor and the non-glycogen phosphoryase inhibiting anti-diabotic agent, or the combination of the glycogen phosphorylase inhibitor and the anti-obesity agent delayed or provented the Male Sprague-Dawley rats (Charles Rivers Labs; Wilmington, MA) weighing 200 g are fed a cafetoria diet mallows, peanut butter, Twinkies, and sweetened condensed milk plus the glycogen phosphorylase inhibitor, the combination of the glycogen phosphorylase Inhibitor and the non-glycogen phosphorylase inhibiting anti-diabotic agent, or the combination of the glycogen phosphorylase inhibitor and the anti-obesity agent (p.o. by gavage or in the diet) or vehicle (untreated) for seven to forty-two days. At the end of the seven to forty-two day period, blood samples are taken for plasma glucose and insulin determination in the fed state. Body weight and adjoose depot weight are also determined. A reduction in plasma glucose or insulin levels in the fed state, and/or lower glucose or insulin levels during anti-diabetic agent, or the combination of the glycogen phosphorylase inhibitor and the anti-obesity agent pius cafeteria diet-treated group compared to the cafeteria-fed control group will indicate that the glycogen phosphorylase inhibitor, consisting of braunschweiger liver sausage, assorted candy bars, cheeses, cookles, com chips, granola bars, marshonset of Insulin resistance, hyperglycomia, and impaired glucose tolerance induced by the cafeteria diet treatment. 5 5

#### Claims

- Use of a gycogen phosphoryase inhibitor in the manufacture of a medicament for treating prophylactically an individual in whom Type 2 diabotes melitius has not yet presented, but in whom there is an increased risk of developing such condition. ÷ 8
- 2. The use according to claim 1 wherein said increased risk comprises a risk factor associated with a Type 2 diabetes pre-disposing disease state or condition. 53
- The use according to claim 2 wherein said risk factor is selected from the group consisting of: e;
- (i) risk factors associated with classification as an individual having Insulin resistance and/or hyperinsulinemia; risk factors based on environmental or genetic Type 2 diabetes pre-disposing disease states or conditions: (iii) risk factors predicated on race and/or ethnicity;
  - (iv) risk factors based on genetic mutations affecting (3-cell function;
- (v) risk factors based on genetic defects in insulin action;
  (vi) risk factors based on genetic defects in insulin action;
  (vii) risk factors based on presence of excess adipose lissue or clinically diagnosed obesity;
  (viii) risk factors identified through clinical chemistrates or diagnostic testing signifying a pre-diabotic stato;
  (viii) risk factors related to physiologic and endocrine changes associated with growth, development, or aging;
  (ix) risk factors based on abnormal cardiovascular or blood lipid parameters;
  (xi) risk factors based on reproductive status;
  (xii) risk factors attributable to muscle westing;

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- (xiii) risk factors associated with polycystic ovary syndrome;
- (xiv) risk factors due to organ disease or dysfunction;
  (xv) risk factors due to conditions resulting in metabolic disturbances;
  (xvi) risk factors due to endocrine disorders or endocrinopathies;

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- (xvii) risk factors due to pathophysiologic states; (xviii) risk factors factors due to Immune-modiated disease;
- (xx) risk factors associated with having a genetic syndrome assoclated with diabetes; and (xix) risk factors incurred due to drug or chemical exposure;
- (xxi) risk factors associated with the detrimental effects caused by the administration of prolonged, elevated
  - doses of insulin and/or the presence of ketoacidosis.

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Islander population; said risk factor based on genetic mutations affecting (3-cell function comprises a defect on chromosome 12, gene HNF-1α (MODY3), a defect on chromosome 7, gene glucokinase (MODY2), a defect on chromosome 20, gene HNF-4α (MODY1), or a defect in mitochondriai DNA; sald risk factor based on a genetic The use according to claim 3 wherein said risk factor based on an environmental or genetic Type 2 diabetes predisposing disease state or condition comprises a family history of diabetes; said risk factor predicated on race and or ethnicity comprises individual membership in an African-American, Hispanic, Native American, Asian, or Pacific defect in insulin action comprises a genetic mutation leading to Type A insulin resistance, acanthosis nigricans. 4

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syndrome; said risk factor based on reproductive status comprises pregnancy, a history of gestational diabeles, or mecrosomia; said risk factor attributable to muscle wasting comprises risk due to aging, starvation, exposure to anti-gravity anvironments, or paralysis resulting from spinal cord Injury; said risk factor due to organ disease or dystunction comprises liver chrhosis or renal disease, said risk factor due to conditions resulting in metabolic disturbances comprises ketoacidosis; said risk factor due to endocrine disorders or endocrinopathies comprises hyperandrogenism, thyrotoxicosis, hyperthyroidism, insulinoma, glucagonoma, sometostatinoma, aldosteroma. ks or antidepressents, vecor, diazoxide, dilantin, and HIV protease inhibitors; and said risk factor associated with having a genetic syndrome associated with diabetes comprises Down's Syndrome, Klinefeller's Syndrome, Wolr-ram's Syndrome, Freidreich's Syndrome, Huntington's chorea, Laurence-Moon-Bied Syndrome, myotonic dystro-ram's Syndrome, Freidreich's Syndrome, Huntington's chorea, Laurence-Moon-Bied Syndrome, myotonic dystrorak factor ralatad to physiologic or endocrine changes associated with growth, development, comprises classifi-cation as a menopausal, pubescent, or aged individual; sald risk factor related to diet or eating behaviors comprises nervosa or bulemia; said risk factor based on ebnormal cardiovascular or blood lipid parameters comprises hy-pertension, HDL cholesterol levels S 35 mg/dl and/or TG levels ≥ 250 mg/dl, or classification as having metabolic logic state comprises infection, congenital rubella, cytomegalovirus, toxemia, uremia, sepsis, or trauma; said risk gene; said risk factor based on the presence of excess adipose tissue or diagnosed obesity comprises central comprises impaired glucose tolerance, impaired festing glucose, or hyperglycemia relative to normoghycemia; said consumption of high fat or high carbohydrate diets, experiencing prokonged fasting or starvation, or having anorexia Cushing's Syndrome, pheochromocytoma, acromegaly, hypercortisolemia; said risk factor due to a pathophysiolactor due to immune-mediated disease comprises "stiff man" syndrome or the production of anti-Insulin receptor inducing or hyperglycemia-inducing agents comprising glucocorticoids, cytokines, cy-interferon, thyroid hormone TNFq, thiazides, estrogen-containing products, β-blockers, nicotinic acid, serotonin receptor-targeted antipsychotlions in the insulin receptor, IRS proteins, glucose transporters, PC-1, glucokinsse, UCP-1, β3 adrenergic receptor obesity; said risk factor identified through clinical chemistries or diagnostic testing signifying a pre-diabetic state antibodies; said risk factor incurred due to drug or chemical exposure comprises treatment with insulin-resistance eprechaunism, Rabson-Mendenhall syndrome, lipoatrophic diabetes or condition, or a genetic mutation or muta phy, porphyria, Prader-Willi Syndrome, and Alzheimer's Disease.

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The use according to claim 1 wherein said glycogen phosphorylase inhibitor is selected from the group consisting of:

(I) a compound of formula (I)

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the streoisomers and prodrugs thereof, and the pharmaceutically acceptable salts of said compounds, ster-eoisomers, and prodrugs, wherein:

the dotted line (---) is an optional bond;

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A is -C(H)=, -C((C<sub>1</sub>-C<sub>4</sub>)altyy)= or -C(halo)= when the dotted line (-) is a bond, or A is methylene or -CH((C,-C,)alky)), when the dotted line (-) is not a bond; Rt, Rt<sub>10</sub> or Rt<sub>11</sub> are each independently H, halo, 4-, 6- or 7-nitro, cyeno, (C<sub>1</sub>-C<sub>4</sub>)alky), (C<sub>1</sub>-C<sub>4</sub>)alkoxy, fluoromethyl, difluoromethyl or trifluoromethyl;

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R₄ is H, meihyl, ethyl, n-propyl, hydroxy(C₁-C₃Jalkyl, (C₁-C₃Jalkoxy(C₁-C₃Jalkyl, phenyl(C₁-C₄Jalkyl, phenythydroxy(C₁-C₃Jalkyl, phenyl(C₁-C₄)alkoxy(C₁-C₄Jalkyl, thien-2· or-3·yi(C₁-C₄)alkyl or tur-2· or -3-yi(C,-C,)alkyl wherein said R, rings are mono-, di- or tri-substituted independently on carbon with H, halo, (C1-C4)alkyl, (C1-C4)alkoxy, trifluoromethyl, hydroxy, amino or cyano; or

R<sub>4</sub> is pyrid-2-, -3- or -4-yl(C<sub>1</sub>-C<sub>4</sub>)alkyl, thiazot-2-, -4- or -5-yl(C<sub>1</sub>-C<sub>4</sub>)alkyl, imidazot-1-,-2-, -4- or -5-yl (C<sub>1</sub>-C<sub>4</sub>)alkyl, pyrnot-2- or -3-yl(C<sub>1</sub>-C<sub>4</sub>)alkyl, oxazot-2-, -4- or -5-yl-(C<sub>1</sub>-C<sub>4</sub>)alkyl, pyrazot-3-, -4- or -5-yl-(C<sub>1</sub>-C<sub>4</sub>)alkyl, pyrnazot-3-, -4- or -5-yl-(C<sub>1</sub>-C<sub>4</sub>)alkyl, pyrnazot-3-, -4- or -5-yl-(C<sub>1</sub>-C<sub>4</sub>)alkyl, pyrnazot-3-, -4- or -5-yl-(C<sub>1</sub>-C<sub>4</sub>)alkyl, pyrnazot-3-yl-(C<sub>1</sub>-C<sub>4</sub>)alkyl, wherein said precading R<sub>4</sub> haterocopies are optionally mono- or di-sustituted independently with halo, influoromathyl, (C<sub>1</sub>-C<sub>4</sub>-Balkyl, (C<sub>1</sub>-C<sub>4</sub>-Balkyl, and or hydroxy and said mono-or di-substituents are bonded to carbon;

R<sub>5</sub> is H, hydroxy, fluoro, (C<sub>1</sub>-C<sub>5</sub>)alkyf, (C<sub>1</sub>-C<sub>5</sub>)alkoxy, (C<sub>1</sub>-C<sub>6</sub>)alkanoyf, amino(C<sub>1</sub>-C<sub>4</sub>)alkoxy, mono-Nor di-N.N-(C<sub>1</sub>-C<sub>2</sub>)alikylamino(C<sub>1</sub>-C<sub>2</sub>)alikoxy, carboxy(C<sub>1</sub>-C<sub>2</sub>)alikoxy, (C<sub>1</sub>-C<sub>2</sub>)alikoxy-earbony(IC<sub>1</sub>-C<sub>2</sub>) alikoxy, benzyloxycarbony(IC<sub>1</sub>-C<sub>2</sub>)alikoxy, or carbonyloxy wherein said carbonyloxy is carbon-carbon linked with phenyl, thiazolyl, imidazolyl, 1H-indolyl, furyl, pyrrolyl, oxazolyl, pyrazolyl, isoxazolyl, isothiazolyi, pyridazinyi, pyrimidinyi, pyrazinyi or 1,3,5-triazinyi and wherein said preceding R<sub>5</sub> rings are optionally mono-substituted with halo, (C<sub>1</sub>-C<sub>4</sub>)alkyi, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, hydroxy, amino or trifluoromethyl and said mono-substituents are bonded to carbon;

R<sub>7</sub> is H, fluoro or (C<sub>1</sub>-C<sub>5</sub>)alkyl; or R<sub>5</sub> and R<sub>7</sub> can be taken together to be oxo;

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Re is carboxy, (C1-C8)alkoxycarbonyl, C(O)NReR9 or C(O)R12,

thienyl, turyi, pyrnotyl, pyrnotidinyl, oxazotyl, thiazotyl, imidazotyl, pyrazotyl, pyrazolinyl, pyrazolidinyl, Isoxazotyl, Isothiazotyl, pyranyl, pipendinyl, morpholinyl, pyrdazlnyl, pyrimidinyl, pyrazlnyl, ppenazlnyl or 1,3,5-triazinyl wherein sald preceding R<sub>g</sub> rings are carbon-nitrogen linked; or R<sub>9</sub> is H, (C<sub>1</sub>-C<sub>2</sub>)alkyl, hydroxy or (C<sub>1</sub>-C<sub>3</sub>)alkoxy; and R<sub>9</sub> is H, (C<sub>1</sub>-C<sub>8</sub>)alkyl, hydroxy, (C<sub>1</sub>-C<sub>8</sub>)alkoxy, methytene-perfluorinatod(C<sub>1</sub>-C<sub>8</sub>)alkyl, phenyl, pyridyl,

R<sub>9</sub> is mono-, di- or tri-substituted (C<sub>1</sub>-C<sub>2</sub>)alkyl, wherein said substituents are independently H, hydroxy, amino, mono-N- or di-N, N-(C<sub>1</sub>-C<sub>2</sub>)alkylamino; or

R<sub>9</sub> is mono- or di-substituted (C<sub>1</sub>-C<sub>5</sub>)alkyi, wherein sald substituents are independently phenyi, pyrkbyi, uryl, pyrrolyl, pyrrolidinyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, isoxazolyi, isothiazolyi, pyranyi, pyridinyi, ptperidinyi, morpholinyi, pyridazinyi, pyrimidinyi, pyrazinyi, ptperazinyl or 1,3,5-triazinyl

wherein the nonaromatic nitrogen-containing  $R_\theta$  rings are optionally mono-substituted on nitrogen with  $(C_1-C_\theta)$ alky, benzyl, benzyl, benzoyl or  $(C_1-C_\theta)$ alkoxycarbonyl and wherein the  $R_\theta$  rings are optionally mono-substituted on carbon with halo,  $(C_1-C_\theta)$ alkyl,  $(C_1-C_d)$ alkoxy, hydroxy, amino, or mono-N- and dI-N,N (Cq-C₅)alkylamino provided that no quaternized nitrogen is included and there are no nitrogon-

oxygen, nitrogen-nitrogen or nitrogen-halo bonds; R<sub>12</sub> is piperazin-1-yf, 4-(C<sub>1</sub>-C<sub>4</sub>)alkylpiperazin-1-yf, 4-formylpiperazin-1-yf, morpholino, thlomor-1,1-dloxo-thlazolidin-3-yl, 2-(C1-C6)alkoxycarbonylpyrrolidin-1-yl, oxazolidin-3-yl or 2(R)-hy-1,1-dioxo-thiomorpholino, thiazolidin-3-yl, 1-oxothiomorpholino,

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droxymethylpyrrolldln-1-yl; or

R<sub>12</sub> is 3- and/or 4-mono-or di-substituted oxazetidin-2-y1, 2-, 4-, and/or 5- mono- or di-substituted oxazolidin-3-yl, 2, 4, andor 5-mono- or di-substituted thiazolidin-3-yl, 2, 4, andor 5-mono- or di-substitutod 1-oxothiazolidin-3-yl, 2, 4, and/or 5-mono- or di-substituted 1,1-dioxothiazolidin-3-yl. eridin-1-yl, 3-, 4-, and/or 5- mono-, di-, or tri-substituted piperazin-1-yl, 3-substituted azetidin-1-yl, 4and/or 5-, mono- or di-substituted 1,2-oxazinan-2-yl, 3-and/or 4-mono- or di-substituted pyrazolidin-I-yl, 4- and/or 5-, mono- or di-substituted isoxazolidin-2-yl, 4-and/or 5-, mono- and/or di-substituted sothiazolidin-2-yl wherein said R<sub>12</sub> substituents are independently H, halo, (C<sub>1</sub>-C<sub>5</sub>)-alkyl, hydroxy, amino, mono-N- or di-N,N-(G,-C<sub>2</sub>)alkylamino, !ormyl, oxo, nydroxyimino, (G,-C<sub>2</sub>)alkoxy, сагоху, саг-bamoyi, mono- N-or di-N,N-(G,-C₄)alkylcarbamoy!, (G<sub>1</sub>-C<sub>4</sub>)alkoxyimino, (G,-C₄Jalkoxymathoxy, (G<sub>1</sub>-3- and/or 4-, mono- or di-substituted pyrrolidin-1-yl, 3-, 4- and/or 5-, mono-, di- or tri-substituted pip-Ce)alkoxycarbonyl, carboxy(C1-C5)alkyl or hydroxy(C1-C5)alkyl;

(ii) a compound of formula (ii)

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the storeoisomers and prodrugs thereof, and the pharmaceulically acceptable salts of said compounds, stereolsomers, and prodrugs, wherein:

the dotted line (---) is an optional bond;

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A is -CH(Cq-C\_a)alky()=, -C(halo)= or -N=, when the dotted line (--) is a bond, or A is methylene or -CH((Cq-C\_a)alky()-, when the dotted line (--) is not a bond;
A1, R1, or R1,1 are each independently H, halo, cyano, 4-, 6-, or 7-nitro, (Cq-C\_a)alky(), (Cq-C\_a)alkoyy.

luoromethyl, difluoromethyl or trifluoromethyl;

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R<sub>3</sub> is H or (C<sub>1</sub>-C<sub>5</sub>)alkyl;

R<sub>4</sub> is H, methyl, ethyl, n-propyl, hydroxyl(G<sub>1</sub>-G<sub>2</sub>Jalkyl, (G<sub>1</sub>-G<sub>2</sub>Jalkoxy(G<sub>1</sub>-G<sub>2</sub>Jalkyl, phenyl((G<sub>1</sub>-G<sub>4</sub>Jalkyl, phenyl)((G<sub>1</sub>-G<sub>2</sub>Jalkyl, phenyl)((G<sub>1</sub>-G<sub>2</sub>Jalkyl, phenyl)((G<sub>1</sub>-G<sub>2</sub>Jalkyl, phenyl)((G<sub>1</sub>-G<sub>2</sub>Jalkyl, phenyl)((G<sub>1</sub>-G<sub>2</sub>Jalkyl, phenyl)(G<sub>1</sub>-G<sub>2</sub>Jalkyl, phenyl)(G<sub>1</sub>-G<sub>2</sub>Jalkyl, whenein sall A<sub>1</sub> rings are monoto- di- or thestibatiused independently on carbon with H, halb, (G<sub>1</sub>-G<sub>2</sub>Jalkyl, (G<sub>1</sub>-G<sub>2</sub>Jalkoxy, influoromathyl, hydroxy, amino, cyano or 4,5-dihydro-1H-

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R<sub>4</sub> is pyrid-2; .3- or 4-yi(C<sub>1</sub>-C<sub>4</sub>)alikyl, thiazot-2; .4- or 5-yi(C<sub>1</sub>-C<sub>4</sub>)alkyl, imidazot-2; .4- or 5-yi(C<sub>2</sub>-C<sub>4</sub>)alkyl, cycaol-2; .4- or 5-yi(C<sub>2</sub>-C<sub>4</sub>)alkyl, pyrid-2; .4- or 5-yi(C<sub>2</sub>-C<sub>4</sub>)alkyl, pyrid-2; .4- or 5-yi(C<sub>2</sub>-C<sub>4</sub>)alkyl, isopazot-3; .4- or 5-yi(C<sub>2</sub>-C<sub>4</sub>)alkyl, isopazot-3; .4- or 5-yi(C<sub>2</sub>-C<sub>4</sub>)alkyl, isopazot-3; .4- or 5-yi(C<sub>1</sub>-C<sub>4</sub>)alkyl, pyrimidin-2; .4-,5- or 5-yi(C<sub>1</sub>-C<sub>4</sub>)alkyl, pyrazin-2 or 3-yi(C<sub>1</sub>-C<sub>4</sub>)alkyl, pyrazin-2 or 3-yi(C<sub>1</sub>-C<sub>4</sub>)alkyl, 13,5-tiazin-2-yl(C<sub>1</sub>-C<sub>4</sub>)alkyl or indol-2-(C<sub>1</sub>-C<sub>4</sub>)alkyl, wherein said preceding R<sub>4</sub> heterocycles are optionally mono- or di-substituted independently with halo, trifluoromethy!, (C<sub>1</sub>-C<sub>4</sub>)alky!, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, amino hydroxy or cyano and said substituents are bonded to carbon; or

R<sub>4</sub> is R<sub>1,5</sub>-carbonyloxymethyl, wherein seid R<sub>15</sub> is phenyl, thiazolyl, imidazolyl, IH-indolyl, Iuryl, pyr-rolyl, oxazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or 1,3,5-triazinyi and wherein said preceding R<sub>15</sub> rings are optionally mono- or di-substituted independently with halo, amino, hydroxy, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy or trifluoromethyl and said mono- or di-substituents are bonded to carbon:

R<sub>s</sub> is H, methyl, ethyl, n-propyl, hydroxymethyl or hydroxyethy

Re is carboxy, (C1-C8)alkoxycarbonyl, benzyloxycarbonyl, C(O)NR9R9 or C(O)R12

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R<sub>8</sub> is H, (C<sub>1</sub>-C<sub>6</sub>)alkyt, cyclo(C<sub>3</sub>-C<sub>6</sub>)alkyt, cyclo(C<sub>3</sub>-C<sub>6</sub>)alkyt(C<sub>1</sub>-C<sub>5</sub>)alkyt, hydroxy or (C<sub>1</sub>-C<sub>8</sub>)alkoxy; and pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl, 1,3,5-triazinyl, benzothiazolyl, benzoxazolyl, benzimidazolył, thlochromanył or tetrahydrobenzothiazolył whereln said heterocycle rings are carbon-nitrogen cycle wherein said heterocycle is pyridyl, furyl, pyrrolyl, pyrrolidinyl, oxazolyl, thiazolyl, imidazolyl pyrazolyl, pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, pyranyl, pyridinyl, piperidinyl, morpholinyl R<sub>9</sub> Is H, cyclo(C<sub>3</sub>-C<sub>6</sub>)alkyl, cyclo(C<sub>3</sub>-C<sub>6</sub>)alkyl(C<sub>1</sub>-C<sub>5</sub>)alkyl, cyclo(C<sub>4</sub>-C<sub>7</sub>)alkenyl, cyclo(C<sub>3</sub>-C<sub>7</sub>)alkyl(C<sub>1</sub> C<sub>5</sub>)alkoxy, cyclo(C<sub>3</sub>-C<sub>7</sub>)alkyloxy, hydroxy, methyleneperfluorinated(C<sub>1</sub>-C<sub>8</sub>)alkyl, phenyl, or a hetero

R<sub>9</sub> is (C₁-C<sub>6</sub>)alkyl or (C₁-C<sub>8</sub>)alkoxy wherein said (C₁-C<sub>6</sub>)alkyl or (C₁-C<sub>6</sub>)alkoxy is optionally monosubstituted with cyclo(C<sub>4</sub>,C-)alken-1-yi, phenyi, thienyi, pyňdyi, furyi, pymolyi, pymolidinyi, oxazolyi, thia-zolyi, knidazolyi, pyrazolyi, pyrazolinyi, pyrazolidinyi, lsoxazolyi, isothlazolyi, pyranyi, piperidinyi, mor-

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pyrazinyi, piperazinyi, 1,3,5-triazinyi or indolyi and wherain said (C<sub>1</sub>-C<sub>8</sub> alky) or (C<sub>1</sub>-C<sub>8</sub> alkoxy αre optionally additionally indopendently mono- or di-substituted with hale, hydroxy, (C<sub>1</sub>-C<sub>5</sub> alkoxy, amino, pholinyl, thiomorpholinyl, 1-oxothiomorpholinyl, 1,1-dloxothiomorpholinyl, pyridazinyl, pyrimidinyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>5</sub>)alkylamino, cyano, carboxy, or (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl; and

alkylamino(C,-C<sub>2</sub>)alkyl, (C,-C<sub>2</sub>)alkoxy(C,-C<sub>2</sub>)alkyl, amino, mono-N- or dt-N,N-(C,-C<sub>2</sub>)alkylamino, oy-ano, carboxy, (C,-C<sub>2</sub>)alkoxycarbonyl, carbamoyl, tormyl or trilluoromethyl and sald R<sub>8</sub> rings may op-tionally be additionally mono- or di-substituted Independently with (C,-C<sub>2</sub>)alkyl or halo;  $C_a)$ alkyl, ( $C_1$ - $C_a)$ alkoxy, hydroxy, hydroxy( $C_1$ - $C_a)$ alkyl, amino( $C_1$ - $C_a)$ alkyl, mono-N- or di-N,N-( $C_1$ - $C_a)$ wherein the R<sub>e</sub> rings are optionally mono- or di-substituted independently on carbon with halo, (C<sub>1</sub>

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ltdin-2-yl, oxazolldin-3-yl, 3,4-dihydrolsoquinolin-2-yl, 1,3-dihydrolsoindol-2-yl, 3,4-dihydro-2H-qul-nol-1-yl, 2,3-dihydro-benzol1,4]oxazin-4-yl, 2,3-dihydro-benzol1,4]-thiazine-4-yl, 3,4-dihydro-2H-qul-noxalin-1-yl, 3,4-dihydro-benzolo[i],2]oxazin-1-yl, 1,4-dihydrobenzolo[i]1,2]oxazin-3-yl, 3,4-dihydro R<sub>12</sub> is morpholino, thlomorpholino, 1-oxothlomorpholino, 1,1-dioxothlomorpholino, thlazolidin-3-yl, l-oxothlazolidin-3-yl, 1,1-dioxothlazolidin-3-yl, pyπolidin-1-yl, piperidin-1-yl, piperazin-1-yl, piperazin-4-yl, azetidin-1-yl, 1,2-oxazinan-2-yl, pyrazolidin-1-yl, Isoxazolidin-2-yl, isothiazolidin-2-yl, 1,2-oxaze benzo[e][1,2]-oxazln-2-yl, 3H-benzo[d]isoxazol-2-yl, 3H-benzo[c]isoxazol-1-yl or azepan-1-yl,

(C<sub>1</sub>-C<sub>2</sub>)alkyi, (C<sub>1</sub>-C<sub>2</sub>)alkoxy(C<sub>1</sub>-C<sub>2</sub>)alkyi, amino(C<sub>1</sub>-C<sub>2</sub>)alkyi, mono-N- or di-N/N-(C<sub>1</sub>-C<sub>2</sub>)alkyiamino (C<sub>1</sub>-C<sub>2</sub>)alkoxyimino or (C<sub>1</sub>-C<sub>2</sub>)alkoxyimino and wherein no more than two substituents are selected from oxo, hydroxyimino or (C<sub>1</sub>-C<sub>2</sub>)alkoxyimino and oxo, hydroxyimino oxo, hydr wherein said R<sub>12</sub> rings are optionally mono., di- or tri-substituted independently with halo, (C<sub>4</sub>-C<sub>2</sub>) bamoyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>5</sub>)alky/carbamoyl, (C<sub>1</sub>-C<sub>8</sub>)alkoxy(C<sub>1</sub>-C<sub>3</sub>)alkoxy, (C<sub>1</sub>-C<sub>5</sub>)alkoxycarbonyl, benzyloxycarbonyl, (C<sub>1</sub>-C<sub>5</sub>)alkoxycarbonyl(C<sub>1</sub>-C<sub>5</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonylamino, carboxy (C<sub>1</sub>-C<sub>5</sub>)alkyl, carbamoyl(C<sub>1</sub>-C<sub>5</sub>)alkyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>5</sub>)alkylcarbamoyl(C<sub>1</sub>-C<sub>5</sub>)alkyl, hydroxy alkyl, (C<sub>1</sub>-C<sub>5</sub>)alkoxy, hydroxy, amino, mono-N- or dl- N,N-(C<sub>1</sub>-C<sub>5</sub>)alkylamino, formyl, carboxy, car

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wherein said  $R_{12}$  rings are optionally additionally mono- or di-substituted independently with  $(C_1 - C_5)$  alkyl or halo; yimino are on nonaromatic carbon; and

(iii) a compound of formuta (III)

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the stereoisomers and prodrugs thereof, and the pharmaceutically acceptable salts of said compounds, ster eolsomers, and prodrugs

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R¹ is (C<sub>1</sub>-C<sub>4</sub>)alkyi, (C<sub>3</sub>-C<sub>7</sub>)cycloalkyi, phenyi or phenyi Independentiy substituted with up to three (C<sub>1</sub>-C<sub>4</sub>) alkyy, (C<sub>1</sub>-C<sub>4</sub>)alkoxy or halogen; R² is (C<sub>1</sub>-C<sub>4</sub>)alkyi optionaliy substituted with up to three fluoro atoms; and

(iv) a compound of formula (IV)

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the stereolsomers and prodrugs thereof, and the pharmaceutically acceptable salts of said compounds, stereoisomers, and prodrugs, wherein:

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Q is aryl, substitued aryl, heteroaryl, or substitued heteroaryl; each Z and X are independently (C, CH or CH<sub>2</sub>), N, O or S;

X1 is NRª, -CH2-, O or S;

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each ---- is Independently a bond or is absent, provided that both ---- are not simiutaneously bonds; it is indropen halogen, -OC<sub>1</sub>-Ogality, -SC<sub>1</sub>-Ogality, -OC<sub>1</sub>-Ogality, -OC<sub>2</sub>-Ogality, -OC<sub>2</sub>-Ogality, -NO<sub>2</sub>-CN, -OC<sub>2</sub>-Ogality, -NO<sub>2</sub>-CN, -OC<sub>2</sub>-Ogality, -NO<sub>2</sub>-CN, -OC<sub>2</sub>-Ogality, -OC<sub>2</sub>-Ogality,

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or absent;

R\$ and R\$ are independently hydrogen, halogen, -C<sub>1</sub>-C<sub>2</sub>alkyl, -CN, -C=C-Si(CH<sub>2</sub>)<sub>3</sub>, -OC<sub>1</sub>-C<sub>2</sub>alkyl, -SC<sub>1</sub>-C<sub>2</sub>alkyl, -CF<sub>2</sub>, -NH<sub>2</sub>, -NH<sub>2</sub>, -C<sub>2</sub>alkyl, -C<sub>2</sub>-C<sub>2</sub>alkyl, -CF<sub>3</sub>, -NH<sub>2</sub>, -C<sub>2</sub>-C<sub>2</sub>alkyl, -C<sub>2</sub>-C<sub>2</sub>alkyl, or C<sub>2</sub>-C<sub>2</sub>alkylyl, or R\$ and R\$ together with the atoms on the ning to which they are attached form a five or aix membered ring containing from 0 to 3 heteroatoms and from 0 to 2 double bonds;

R\* is -C(=O)-A; A is -NR\*R4, -NR\*CH2CH2OR\*,

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васh P<sup>d</sup> is independently hydrogen, С<sub>1</sub>-С<sub>в</sub>аlky), С<sub>1</sub>-С<sub>в</sub>аlkoxy, aryl, substituted aryl, heteroaryl, or substi tuted heteroaryl;

each n is independently 1-3.

each Re is independently hydrogen, -C(=0)ORs, -ORs, -SRs, or -NRsRs: and

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The use according to claim 5 wherein said glycogen phosphorylase inhibitor is a compound of formula (I), a sterø

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eolsomer or prodrug thereof, or a pharmaceutically acceptable salt of said compound, stereolsomer, or prodrug

- The use according to claim 6 wherein said compound of formula (I) is selected from the group consisting of: ۲.
- 5,6-dichloro-1H-indole-2-carboxylic acid-{(15)-[(R)-hydroxy-(methoxy-methylcarbamoyl)-methyl-2-phenyl 5-chloro-1 H-indolo-2-carboxylic acid-[(1S)-((R)-hydroxy-dimathylcarbarnoylmathyl)-2-phanyl-athyl]-amide;
- acid-{(1S)-{(R)-hydroxy-(methoxy-methylcarbamoyl)-methyl]-2-phenyl-5-chloro-1H-Indole-2-carboxylic
  - s-chloro-1H-Indole-2-carboxylic acid-((1S)-((R)-hydroxy-((2-hydroxy-ethyl)-methyl-carbamoyl}-methyl)2-phe-

    - 5-chloro-1H-indole-2-carboxylic acid-((1S)-{(R)-hydroxy-[methyl-(2-pyridin-2-yl-ethyl)-carbamoyl]-methyl}-2-phenyl-ethyl)-amide;
- acid-[(1S)-benzyl-(2R)-hydroxy-3-(4-methylpiperazin-1-yl)-3-oxo-propyl]acid-[(1S)-benzyl-(2R)-hydroxy-3-(3-hydroxyazetidin-1-yl)-3-oxo-propylj-5-chloro-1H-indole-2-carboxylic 5-chloro-1H-Indole-2-carboxylic
- 5-chloro-1H-Indole-2-carboxylic acid-((1S)-benzyl-(2R)-hydroxy-3-isoxazolidin-2-yl-3-oxo-propyl)-amide;
- 5-chloro-1H-indole-2-carboxylic acid-((1S)-benzyl-(2R)-hydroxy-3-(1,2)oxazInan-2-yl-3-oxo-propyl)-amide; 5-chloro-1H-indole-2-carboxylic acid-((1S)-benzyl-(2R)-hydroxy-3-((3S)-hydroxy-pyrralidin-1-yl)-3-oxo-pro-5-chloro-1H-Indole-2-carboxylic acid-[(15)-benzyl-3-((35,45)-dihydroxypyrrolldin-1-yl)-(2R)-hydroxy-3-oxo-
- 5-chloro-1H-Indole-2-carboxylic acid-[(15)-benzyl-3-((3R,4S)-dihydroxypyrrolidin-1-yr)-(2H)-hydroxy-3-oxo-
- 5-chloro-1H-indole-2-carboxylic acid-(1S)-banzyl-(2R)-hydroxy-3-morpholin-4-yl-3-oxo-propyl)-emide; the stereolsomers and prodrugs thereof, and the pharmaceutically acceptable salts of sald compounds, sterpropyl]-amide; and

eolsomers, and prodrugs.

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- The use according to claim 5 wherein said glycogen phosphorylase inhibitor is a compound of formula (II), a stereolsomer or prodrug thereof, or a pharmaceutically acceptable salt of said compound, stereolsomer, or prodrug. 8 30
  - The use according to claim 8 wherein said compound of formula (II) is selected from the group consisting of: 6
- 5-chloro-1H-Indole-2-carboxylic acid-[2-(cls-3,4-dihydoxy-pyro|Idln-1-yl)-2-oxo-ethylj-amide; 5-chloro-1H-indole-2-carboxylic acid-[{1-(s)-benzyl-2-(cis-3,4-dihydroxypyrrolidin-1-yl)-2-oxo-ethylj-amide; 5-chloro-1H-indole-2-carboxylic acid-[2-(1,1-dioxo-thlazolidin-3-yl)-2-oxo-ethylj-amide; 5-chloro-1H-Indola-2-carboxylic acid-{(1S)-benzyl-2-{3-hydroxyiminopyrrolidin-1-yl}-2-oxo-athyl]-amida;

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- 5-chloro-1H-indole-2-carboxylic acid-(2-oxo-2-thiazolidin-3-yl-ethyl)-amide;
- 5-chloro-1H-Indole-2-carboxylic acid-{(1S)-(2-fluoro-benzyl)-2-(4-hydroxyplperidin-1-yl)-2-oxo-ethyl)-amide; 5-chloro-1H-indole-2-carboxylic acid-{15}-(4-fluoro-benzyl)-2-(4-hydroxypperidin-1-yl)-2-oxo-ethyl]-amide; 5-chloro-1H-indole-2-carboxylic acid-{115}-benzyl-2-((3RS)-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide; 5-chloro-1H-indole-2-carboxylic acid-2-oxo-2-((1RS)-oxo-1-thlazolidin-3-yl)-ethyl]-amide; 5-chloro-1H-Indole-2-carboxyllc acid-(1S)-benzyl-2-(3-hydroxy-azetidin-1-yf)-2-oxo-ethyfl-amide
- the stereoisomers and prodrugs thereof, and the pharmaceutically acceptable salts of said compounds, ster-5-chloro-1H-indole-2-carboxylic acid-{(15)-benzyl-2-(3-hydroxyimino-azetidin-1-yl)-2-oxo-ethyl}-amide; and 5-chloro-1H-Indole-2-carboxylic acid-[(1S)-benzyl-2-(4-hydroxylmino-piperidin-1-yl)-2-oxo-ethyl]-amide; eoisomers, and prodrugs.
- stereoisomer or prodrug thereof, or a pharmaceutically acceptable salt of said compound, stereoisomer, or prodrug. The use according to claim 5 wherein said glycogen phosphorylase inhibitor is a compound of formula (III), a 20
- 11. The use according to claim 10 wherein said compound of formula (III) is selected from the group consisting of:
- 5-acetyl-1-ethyl-2-oxo-2,3-dihydro-1H-Indole-3-carboxylic acid (3-(4-bromophenylcarbamoyl-phenyl)-amide 5-acetyl-1-ethyl-2-oxo-2,3-dihydro-1H-indole-3-carboxylic acid (3-p-tolylcarbamoyl-phenyl)-amide;

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5-acetyl-1-ethyl-2-oxo-2,3-dlhydro-1H-Indole-3-carboxylic acid (3-phenylcarbamoyl-phenyl)-amide;

the stereoisomers and prodrugs thereof, and the pharmaceutically acceptable salts of said compounds, ster-

- 12. The use according to claim 5 wherein said glycogen phosphorylase inhibitor is a compound of formula (IV), a stereoisomer or prodrug thereof, or a pharmaceutically acceptable salt of said compound, stereoisomer, or prodrug
- 13. The use according to claim 12 wherein said compound of formula (IV) is selected from the group consisting of:
- (±)-2-bromo-4H-furo[3,2-b]pyrrole-5-carboxylic acid-[1-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-2-bromo-4H-thleno[3,2-b]pyrrole-5-carboxyilc\_acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-2-chloro-6H-thleno[2,3-b]pyrrole-5-carboxylic acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-
- 2-chloro-6H-thieno(2,3-bjpyrrote-5-carboxylic acld-{(1S)-benzyl-2-morpholin-4-yl-2-oxo-ethyf]-amide; 2-chloro-6H-thieno(2,3-bjpyrrote-5-carboxylic acld-{(1S)-benzyl-2-(1,1doxo-1-thiazolidin-3-yf)-2-oxo-ethyflethyl]-amide;
- acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-2-chloro-4H-furo[3,2-b]pyrrole-5-carboxylic ethyl]-amide;
- 3-methyl-4H-thleno[3,2-b]pyrrole-5-carboxyilc acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-2-chloro-4H-furo[3,2-b]pyrrole-5-carboxylic acid-[(1S)-benzyl-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)hy-2-chloro-4H-thleno(3,2-b]pyrrole-5-carboxylic acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxodroxy-3-oxo-propyl]-amide; ethyf]-amide; and

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- the stereoisomers and prodrugs thereof, and the pharmaceutically acceptable salts of said compounds, stereolsomers, and prodrugs. ethyl]-amide;
- 14. Use of a gycogen phosphorylase inhibitor and a non-glycogen phosphorylase inhibiting anti-diabetic agent in the manufacture of a medicament for treating prophylactically an individual in whom Type 2 diabetes mellitus has not yet presented, but in whom there is an increased risk of developing such condition.

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- 15. The use according to claim 14 wherein sald glycogen phosphorylase inhibitor is selected from the group consisting
- 5-chloro-1H-indole-2-carboxylic acid-{(1S)-{(R)-hydroxy-(methoxy-methylcarbamoyi)-methyl]-2-phenyl-ethyl} 5,6-dichloro-1H-indole-2-carboxylic acid-{(1S)-[(R)-hydroxy-(methoxy-methylcarbamoyl)-methyl]-2-phenyl-5-chloro-1H-indole-2-carboxylic acid-{(1S)-((R)-hydroxy-dimethylcarbamoylmethyl)-2-phenyi-ethylj-amide;
  - acid-((1S)-{(R)-hydroxy-{(2-hydroxy-ethyl)-methyl-carbamoyl}-methyl}-5-chloro-1H-indole-2-carboxylic acid-((1S)-((R)-hydroxy-(methyl-(2-pyridin-2-yi-ethyl)-carbamoyl)-methyl)--chloro-1H-indole-2-carboxytic
- acid-[(1S)-benzyi-(2R)-hydroxy-3-(4-methylpiperazin-1-yl)-3-oxo-propyll-5-chloro-1H-indole-2-carboxylic acid-[(1S)-benzyi-(2R)-hydroxy-3-(3-hydroxyazetidin-1 -yl)-3-oxo-propyl 5-chloro-1H-indole-2-carboxylic 2-phenyl-ethyl)-amide;

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5-chloro-1H-indole-2-carboxylic acid-{(1S)-benzyl-(2R)-hydroxy-3-{(3S)-hydroxy-pyrrolidin+1-yl)-3-oxo-pro-5-chloro-1H-Indole-2-carboxylic acid-((1S)-benzyi-(2R)-hydroxy-3-[1,2]oxazinan-2-yi-3-oxo-propyl)-amide; 5-chloro-1H-Indole-2-carboxyllc acid-((1S)-benzyl-(2R)-hydroxy-3-lsoxazoildin-2-yl-3-oxo-propyl)-amide;

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- 5-chloro-1H-indole-2-carboxylic acid-[(1S)-benzyl-3-((3S,4S)-dihydroxypyrrolidin-1-yl)-(2R)-hydroxy-3-oxopropyi]-amide;
  - 5-chloro-1H-indole-2-carboxylic actd-[(1S)-benzyl-3-((3R,4S)-dihydroxypyrrolidin-1-yl)-(2R)-hydroxy-3-oxopropyl]-amide;

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5-chloro-1H-indoie-2-carboxylic acid-(1(5)-benzyi-(2R)-hydroxy-3-morpholin-4-yi-3-oxo-propyi)-amide; 5-chloro-1H-indoie-2-carboxylic acid-(1(15)-benzyi-2-(3-hydroxyiminopyrrolidin-1-yi)-2-oxo-ethylj-amide;

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5-acetyr.1-ettry/2-oxo-2,3-dliydro-1H-Indole-3-aarboxylic acid (3-(4-bromophany/carbamoyl-phanyl)-amide; 5-acetyr.1-ettry/2-oxo-2,3-dliydro-1H-Indole-3-carboxylic acid (3-pheny/carbamoyl-phenyl)-amide; 2-chloro-6H-thieno(2,3-bjpyrrole-5-carboxylic acid-{(15)-banzyl-2-{(3R,4S)-dliydroxy-pyrrolldin-1-yl)-2-oxo-5-chloro-1H-indole-2-carboxylic acid-[(1S)-(2-fluoro-benzyl)-2-(4-hydroxypiperidin-1-yl)-2-oxo-ethyl]-amide 5-chioro-1H-indole-2-carboxylic acid-(1S)-(4-fluoro-benzyl)-2-(4-hydroxypipendin-1-yl)-2-oxo-ethylj-amide 5-chloro-1H-indole-2-carboxylic acid-[(1S)-benzyl-2-(cis-3,4-dihydroxypyrrolidin-1-yl)-2-oxo-ethyl]-amlde; 5-chioro-1H-indole-2-carboxylic acid-[(15]-banzyl-2-(3-hydroxylmino-azatidin-1-yi)-2-oxo-eithyll-amide; 5-chioro-1H-indole-2-carboxylic acid-[(15]-banzyl-2-(4-hydroxylmino-pipendin-1-yi)-2-oxo-eithyll-amide; 5-acetyl-1-eithyl-2-oxo-2,3-dihydro-1H-indole-3-carboxylic acid (3-p-tolylcarbamoyl-pheny)-amide; 5-chioro-1H-indole-2-carboxylk acld-{(1S)-benzyl-2-((3RS)-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide; 5-chloro-1H-Indoie-2-carboxylic acid-(1S)-benzyi-2-(3-hydroxy-azetidin-1-yl)-2-oxo-ethyl}-amide; 5-chioro-1H-indole-2-carboxylic acid-[2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 5-chloro-1H-indole-2-carboxylic acid-2-oxo-2-((1RS)-oxo-1-thiazolidin-3-yl)-ethyl]-amide; 5-chioro- 1H-indole-2-carboxylic acid-[2-(1,1-dloxo-thiazolidin-3-yi)-2-oxoethyi]-amide; 5-chioro-1H-indoie-2-carboxylic acid-(2-oxo-2-thiazolidin-3-yf-ethyl)-amide;

(±)-2-bromo-4H-furo[3,2-b]pyrrole-5-carboxylic acid-[1-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-

ethyl]-amide;

2-bromo-4H-thleno[3,2-b]pyrrole-5-carboxyllc acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolldin-1-yl)-2-oxoethyl]-amide;

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2-chloro-6H-thieno[2,3-bjpyrrole-5-carboxylic acid-{(1S)-benzyl-2-morpholin-4-yl-2-oxo-ethylj-amide; 2-chloro-6H-thieno[2,3-bjpyrrole-5-carboxylic acid-{(1S)-benzyl-2-{(1,1doxo-1-thiazoiidin-3-yl)-2-oxo-ethylj-2-chloro-4H-furo[3,2-b]pyrrole-5-carboxylic acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-

o-4H-furo[3,2-b]pyrroie-5-carboxylic acid-{(1S)-benzyl-3-{(3R,4S)-dihydroxy-pyrrolidin-1-yl)-{2R)hydroxy-3-oxo-propyf]-amide; ethyl]-amide;

2-chioro-4H-thieno[3,2-b]pyrrole-5-carboxylic acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolldin-1-yl)-2-oxo-

3-methyl-4H-thieno[3,2-b]pyrrole-5-carboxyilc acld-[(1S)-benzyi-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxoethyl]-amide; the stereoisomers and prodrugs thereof, and the pharmaceutically acceptable salts of said compounds, stereoisomers, and prodrugs; and ethyl]-amide; and

aniagonist, a glucagon antagonist, a growth hormone eecretagogue, a gluconeogenesis inhibitor, a somato-statin anaiog, an antilipolytic agent; a lipoxygenasa inhibitor; an irsulin signaling agonist; an Insulin mimetic; a PTP1B inhibitor; an insulin degrading enzyme inhibitor; and a glycogen synthase kinase Inhibitor. sald non-glycogen phosphorylase inhibiting anti-diabetic agent is selected from the group consisting of D-chirolnositol; insulin or an insulin analog, GLP-1 (7-37) (insulinotropin) or GLP-1 (7-36)-NH $_2$ , an  $\alpha$ -glucosidase inhibitor, a giltazone and/or an insulin sensitizer, a sulfonylurea or an analog thereof, a biguanide, an  $lpha_2$ a β-agonist, a phosphodiesterase inhibitor, a lipid-lowering agent, a vanadate or vanadium complex, an amylin antagonist or imidazoline, an insulin secretagogue, an aidose reductase inhibitor, a fatty acid oxidation inhibito

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6-phosphatasa inhibitor or GP 3034; said antilipolytic agent is solected from the group consisting of nicotinic acid, aciptmox, and WAG 994; said amylin antagonist is pramilintide or AC-137; said glucagon antagonist is BAY 27-8956; said lipoxygenase inhibitor is masoprocol; and said insuiin signaling agonist is L-783281. said gitazone and/or insulin sensitizer is selected from the group consisting of cigiliazone, piogitiazone, engilita-zone, trogiliazone, dargitiazone, rosigiitazone, JTT-501, MCC-555, and MX 6054; said suifonyluree or analog theroof is selected from the group constiting of chlorpropamide, glibenciamide, tobutamide, tolazamide, acotoof midagiazole, isagiidole, derigiidole, idazoxan, efaroxan, and fitparoxan; said insulin secretagogue is selected from the group consisting of inoglinde, A-4165, exendin-4, and BTS-87582; said aidose reductase inhibitor is inhibitor is L-386,398; said lipid-lowering agent is benfluorex; said vanadate or vanadium complex is selected from 16. The use according to cialm 15 wherein said insulin analog is LysPro Insulin; said a-giucosidase inhibitor is selected from the group consisting of acarbose, voglibose, miglitol, emigiltate, camigibose, MDL-25,637, and MDL-73,945 hexamide, giipizide, giimepiride, repaglinide, and meglitinide; said biguanide is selected from the group consisting selected from the group consisting of epairestat, sorbinil, toirestat, zenarestat, and zopoirestat; said fatty acid oxidation inhibitor is selected from the group consisting of clomoxir and etomoxir; said eta-agonist is selected from the group consisting of BRL-35135, BRL-37344, TAK-37344, AZ 40140, and CL 316,243; sald phosphodiesterase the group consisting of naglivan and peroxovanadium complexes; said gluconeogenesis inhibitor is a glucoseof metformin, phenformin, and buformin; said  $lpha_2$ -antagonist or imidazoline is selected from the group consistir

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- 17. Use of a glycogen phosphorylase inhibitor and an anti-obesity agent in the manufacture of a medicament for treating prophylactically an individual in whom Type 2 diabetes mellitus has not yet presented, but in whom there is an increased risk of developing such condition.
- The use according to claim 17 wherein said glycogen phosphorylase inhibitor is selected from the group consisting
  of:

5-chloro-IH-holole-2-carboxylic acid-{(1S)-\((R)-hydroxy-dimethylcarbamoyimethyl)-2-phenyi-ethyl-arhide; 5-6-defunco IH-indole-2-carboxylic acid-\((1S)-\((R)-hydroxy-(methoxy-methycarbamoyi)-methyl-2-phenyi-arhid-arhide;

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any frames, any frames, 5-chloro : H-Indole-2-carboxylic acid-{(1S)-{(R)-hydroxy-(methoxy-methy/carbamoyl)-methylj-2-phenyleltylj-amide;

5-chloro-1H-Indole-2-carboxylic acid-((1S)-(IR)-Inydroxy-(I2-hydroxy-ethyl)-methyl-2-phemyd-dhyly-amidide; 5-chkoro-1H-Indole-2-carboxylic acid-((1S)-(IR)-hydroxy-fronthyl-2-carbolic 2-d-hydroxyll-amidide).

5-chloro-1H-indole-2-carboxylic acid-((1S)-((R)-tydroxy-(methyl-(2-pyridin-2-yl-ainyl)-carbamoyij-mathyl)
2-phonyl-einyly-amidio;
5-chloro-1H-indole-2-carboxylic acid-((1S)-benzyl-(2R)-tydroxy-3-(4-methylpiperazin-1-yl)-3-oxo-propyl)-amide;

5-chloro-1H-Indole-2-carboxylic acid-((1S)-benzyl-(2R)-hydroxy-3-(3-hydroxyazetidin-1-yl)-3-oxo-propyl)amide:

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5-chloro-1H-indole-2-carboxylic acid-((1S)-benzyl-(2R)-hydroxy-3-isoxazolidin-2-yl-3-oxo-propyl)-amide; 5-chloro-1H-indole-2-carboxylic acid-((1S)-benzyl-(2R)-hydroxy-3-(1,2)vazhlnan-2-yl-3-oxo-propyl)-amide; 5-chloro-1H-indole-2-carboxylic acid-((1S)-benzyl-(2R)-hydroxy-3-((3S)-hydroxy-pyrrolidin-1-yl)-3-oxo-propyll-amide;

pył amide: 5-chioro-1H-indole-2-carboxylic acid-{(18}-benzyl-3-{(185.4S)-dihydroxypyrrolidin-1-yr)-{2R}-hydroxy-3-oxopropyl-amide;

5-chloro-1 H-indole-2-carboxylic acid-{(1S)-benzyl-3-((3R,4S)-dihydroxypyrrolidin-1-y/)-{2R)-hydroxy-3-oxo-propyl-amide;

5-chloro-1H-indole-2-carboxylic acid-{(15)-benzy-(2R)-hydroxy-3-morpholin-4-yi-3-oxo-propy)-amide; 5-chloro-1H-indole-2-carboxylic acid-{(15)-benzy-{(24)-yydroxy-morpholin-4-yi-3-oxo-athyl-amide; 5-chloro-1H-indole-2-carboxylic acid-{(15)-benzy-12-ditydroxy-pyrmolidin-1-yi)-2-oxo-athyl-amide; 5-chloro-1H-indole-2-carboxylic acid-{(15)-benzy-12-ditydroxy-pyrmolidin-1-yi)-2-oxo-athyl-amide; 5-chloro-1H-indole-2-carboxylic acid-{(2-(1-)-4-benzy-12-ditydroxy-pyrmolidin-1-yi)-2-oxo-athyl-amide; 5-chloro-1H-indole-2-carboxylic acid-{(2-(1-)-4-benzy-12-dityd-amide)}
5-chloro-1H-indole-2-carboxylic acid-{(2-(1-)-4-(1-)-4-benzy-12-dityd-amide)}
5-chloro-1H-indole-2-carboxylic acid-{(2-(1-)-4-(1-)-4-benzy-12-dityd-amide)}
5-chloro-1H-indole-2-carboxylic acid-{(2-(1-)-4-(1-)-4-benzy-12-dityd-amide)}
5-chloro-1H-indole-2-carboxylic acid-{(2-(1-)-4-(1-)-4-benzy-12-dityd-amide)}
5-chloro-1H-indole-2-carboxylic acid-{(2-(1-(1-)-4-(1-)-4-(1-)-4-(1-)-4-(1-)-4-(1-)-4-(1-)-4-(1-)-4-(1-

Schloro Hindole 2-carboxyle acid-(1 s)-cells-(1-class-4-clatifux) daypylamide; b-chloro Hindole 2-carboxyle acid-(1 s)-cells-(1 class-6-clatifux) daypylamide; b-chloro Hindole 2-carboxyle acid-(2 vo.2-thiazolidin-3-yl)-2-voc-ahyl-amide; b-chloro Hindole 2-carboxyle acid-(1 s)-4-chloro-barzyl-2-(4-bity)-amide; b-chloro Hindole 2-carboxyle acid-(1 s)-4-chloro-barzyl-2-(4-bity)-amide; b-chloro Hindole 2-carboxyle acid-(1 s)-4-chloro-barzyl-2-(4-bity)-amide; b-chloro-Hindole 2-carboxyle acid-(1 s)-2-chloro-hindole 2-chloro-hindole 2-carboxyle acid-(1 s)-2-chloro-hindole 2-chloro-hindole 2-chloro-hindole

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(±)-2-bromo-4H-lura[3,2-b]pyrrola-5-carboxylic acid-{1-benzyl-2-{(3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-eihyl)-amide;

2-bromo-4H-thlano[3,2-b]pymole-5-carboxylic acid-{(1S}-benzyl-2-((3R,4S)-dihydroxy-pymolidin-1-yl)-2-oxoethylj-amide;

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2-chloro-6H-thieno[2,3-b]pyrrolo-5-carboxylic acid-{(15)-benzyl-2-norpholin-4-yl-2-oxo-ethyl-amide; 2-chloro-6H-thieno[2,3-b]pyrrolo-5-carboxylic acid-{(15)-benzyl-2-(1,1dloxo-1-thiazolidin-3-yl)-2-oxo-ethyl-amide;

2-chloro-4H-iun[3,2-b]pymole-5-carboxylic acid-{(1S}-banzyh-2-{(3R,4S}-dihydroxy-pymolidin-1-yi)-2-oxo-ethyll-amide; 2-chloro-4H-tun[3,2-b]pymole-5-carboxylic acid-{(1S}-banzyh-3-{(3R,4S}-dihydroxy-pymolidin-1-yi)-{2R}hy-

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2-chloro-4H-thleno[3,2-b]pyrrole-5-carboxylic acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-

droxy-3-oxo-propyl]-amide;

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#### ethyl]-amide; an

3-mathyl-4H-thleno[3,2-b]pyrrole-5-carboxylic acid-{(1 S}-benzyl-2-{(3R,4S}-dihydroxy-pyrrolidn-1-yl)-2-oxoothyl-aride; ne teareolsomera and pordugs thereol, and the pharmaceutically acceptable salts of said compounds, stereolsomera, and pordugs, and

said anti-obesity agent is selected from the group consisting of a β-adranargic receptor agonist, an apolipoprotein-La Secretiforn/incrosomal tridyperdot brancher protein inhibitic, an MCFA-agonist, a cholocystokinin-A
agonist, a monoamine reuptake inhibitor, a sympathiominatic agent, a serotioninargic agent, a carcitoninargic agent, a cancininargic agent, a cancininargic agent, a cancininargic, a melano-cyte-etimulating hormone anceptor agonist or mimetic, a melano-cyte-etimulating hormone anceptor agonist, a canneablorid receptor antigonist, a legible or an analogot thereof, a galantin antiagonist, a lipsea inhibitor, an anoracide agent, a Neuropeptide-Y antiagonist, a thyronimetic agent, a dehydroeplandrosterone or an analog thereof, a glucocorticoid roceptor agonist or antagonist, an oracidir brinding protein antiagonist, a glucagon-like peptide-1 receptor agonist, a callary neurotrophic facetor, and an AGRIP antiagonist.

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- 19. The use according to claim 18 wherein said anti-obasity agent is selected from the group consisting of phentermine, ephodinic, pictin, phenypropanolarinic, and pseudosphedrine; asid (3-adranegic receptor agents) as selected from the group constitution of (4-(2-(2-(6-antinopyridin-3-yij-2-(R)-tydroxyethylanino)sutavy)phenylylacetic scid, (4-(2-(2-(6-antinopyridin-3-yij-2-(R)-tydroxyethylanino)sutavy)phenylylacetic scid, (and (4-(2-(2-(6-antinopyridin-3-yij-2-(R)-tydroxyethylanino)sutavy)phenylylacetic scid; and monearnine reuptake inhibitor is abulramine; and serotoninergic agent is ferifuramine or dexfenifuramine asid doparnine agonis is bronocriptine; said lipase inhibitor is oritista; and said anorectic agent is anothered anorectic agent is anothered.
- 20. A pharmacautical composition comprising a giycogen phosphorylase inhibitor and a non-giycogen phosphorylase inhibiting anti-diabetic agent.
- 21. A pharmaceutical composition comprising a glycogen phosphorylase inhibitor and an anti-obesity agent
- 22. A pharmacautical product containing a glycogen phosphorylase inhibitor and a non-glycogen phosphorylase inhibitor and reladiate species as combined preparation for simultaneous, separatio or sequential use in treating prophylactically an individual in whom Type 2 diabetes mellitus has not yet presented, but in whom there is an increased risk of developing such condition.
- 23. A pharmaceutical product containing a glycogen phosphorylase inhibitor and an anti-obesity agent as a combined propriatation for simultaneous, separate or sequential use in treating prophylactically an individual in whom Typo 2 diabetes mellitus has not yet presented, but in whom there is an increased risk of developing such condition.

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**EUROPEAN PATENT APPLICATION** Ξ

(88) Date of publication A3: 26.03.2003 Bulletin 2003/13

(43) Date of publication A2: 26.09.2001 Bulletin 2001/39

(51) Int C.P. AG1K 31/00, AG1K 31/404, AG1K 31/4439, AG1K 31/496, AG1K 31/422, AG1K 31/5377, AG1K 31/427, AG1K 31/454, AG1K 31/407, AG1K 45/06, AG1P 3/10

(22) Date of filing: 05.03.2001

(21) Application number: 01301979.9

(84) Designated Contracting States:
AT B C H CY DE DK ES FI FR QB GR IE IT LI LU
MC NL PT SE TR
MC NL PT SE TR Designated Extension States: AL LT LV MK RO SI

(72) Inventor: Treadway, Judith Lee Groton, Connecticut 06340 (US)

(74) Ropresentative: Hayles, James Richard Prizer Limited. Patents Department, Ramsgate Road Sandwich Kent CT13 9NJ (GB) (30) Priority: 22.03.2000 US 191381 P

(54) Use of glycogen phosphorylase inhibitors (71) Applicant: Pfizer Products Inc. Groton, CT 06340-5146 (US)

(57) Individuats in whom Type 2 diabetes meilitus has not lygoresoland, but whom there is an invesessed risk of developing such condition, can be treated prophylactically with a glycogen phosphorylass inhibitor, a

głycogen phosphorylase inhibitor and a non-glycogen phosphorylase inhibiting anti-diabetic agent; or a głycogen phosphorylase inhibitor and an anti-obesity agent.

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European Patent Office

PARTIAL EUROPEAN SEARCH REPORT Application human withol under fine 4 of the European Potent Communition (E. 8) 39 1979 brosedings, as the European earth report to the purpose of these guest proceedings, as the European search report.

		DOCUMENTS CONSIDERED TO BE RELEVANT	TO BE RELEVANT		
	Category	Chatlon of document with indostion, where appropriate, of relevant passages	rhere appropriate,	Referent	CLASSECATION OF THE APPLICATION DECKY
	×		.) 8 line	1-5,10, 11,14-23	< < < <
	×	WO 96 33384 A (TREADMY JUDITH L :HULLI BERNARD (US); HOOVER DENNIS J (US); PF 12 December 1996 (1996-12-12) Page 5 line 11-14, page 19 line 27-31, page 22 line 5-6, claims 47 and 55	N 1ZE)	1-9, 14-23	A61K31/422 A61K31/5377 A61K31/427 A61K31/464 A61K31/407 A61K45/06
	ш	EP 1 088 824 A (PFIZER PROD INC) 4 April 2001 (2001-04-04) Page 12 line 5-6, page 13 line 36 8, claim 10, claim 13-15	Ē	1-5, 12-23	A61P55/50
					TECHNICAL PELDS BEARCHED (MICLY)
					A61K A61P
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European Patent Office

INCOMPLETE SEARCH SHEET C

Application Number EP 01 30 1979

Claim(s) searched incompletely:

Reason for the limitation of the search:

Present claim 1 relates to a use of a compound for the prophylactically treatment of Type 2 diabetes which is defined by reference to a desirable characteristic or property, namely

- "glycogen phosphorylase inhibitor"

Claims 1-4, 17, 20-23 cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 84 EPC from only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clairty (Article 84 EPC). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. The term "glycogen hosphorylase inhibitor" is open-ended as it may relate to a large number of possible compounds already existing which are glycogen phosphorylase inhibitors, but so far not identified as such consequently, the search has been compounds already existing which are glycogen phosphorylase inhibitors, but so far not identified as such consequence to be clear, supported and disclosed, namely those parts relating to the compounds specified in claims 5-13.

 the expression: "non-glycogen phosphorylase inhibiting anti-diabetic agent" in claim 14, 26, 22 and (Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to compounds, specified in claims 15-16)

- "an anti-obesity agent" in claims 17, 21 and 23

(Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to compounds, specified in claim 19)

the skilled person is unable to determin unambiguously which compounds fall under the scope of the expressions:

an alpha-glucosidase inhibitor, an insulin analog, a glitazone or an
insulin sensitizer, a sulfonylurea or an analog thereof, a biguanide, an
alpha2-antagonist or imidazoline, an insulin serretagogue, an aldoser
reductase inhibitor, a fatty acid oxidation imhibitor, a beta-agonist, a
phosphodiesterase inhibitor, a lipid-lowering agent, a vanadate or
vanadium complex, an anylin antagonist, a glucagon antagonist, a growth
hormone secretagogue, a gluconeogenesis inhibitor, a somatostatin analog,

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INCOMPLETE SEARCH SHEET C

an antilipolytic agent, a lipoxygenase inhibitor, an insulin signaling agonist, an insulin mimetic, a PTP18 inhibitor, an insulin degrading enzyme inhibitor and a glycogen synthase kinase inhibitor in claim 15, and

(Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to compounds, specified in claims 16)

- the terms " beta-adrenergic receptor agonist, an apolipoprotein secretion/incrosomal triglyceride transfer protein inhibitor, an MCR-4 agonist, a cholecystokinin-A agonist, a monamine reuplexe inhibitor, a sympathiomimetic agent, a dopamine agonist, a melanocyte-stimulating hormone receptor agonist or mimetic. a melanocyte-stimulating hormone nealing, a melanin concentrating hormone antagonist, a cannablinoid receptor antagonist, leptin or an analog therof, a galanin antagonist, a lipses inhibitor, an anorectic agent, a theropettide-Y antagonist, a thyrodimetic agent, a dehydroepiandrosterone or an analog therof, a glucacorticoid receptor agonist or antagonist, an orexin receptor antagonist, a uncoorticoid receptor agonist or antagonist, an glucagon-like peptifide-I receptor agonist, a ciliary neurotrophic factor, and an AGRP antagonist in claim 18, and

(Consequently, the search has been carried out for those parts of the calms which appear to be clear, supported and disclosed, namely those parts relating to compounds, specified in claims 19)

the term "a bombesin agonist" in claim 19

(Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, mamely those parts relating to compounds, specified in claim 19).

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO.

This area is the potent timely number or eleting to the potent documents cited in the above-mentioned European eserch report.
The members are as contained in the European Pleant Office EDP has on.
The European Pleant Office is in no way faithe for these particulars within are marely given for the purpose of information.

29-01-2803

NO 9639384 A 12-12-1999 NONE  NO 9639384 A 12-12-1996 CA 2224662 A1 12-12-18  AP 6233 A 1 12-12-18  AU 546266 A 112-12-18  BU 546266 A 31-12-18  BU 546266 A 31-12-18  BU 144449 A 12-12-18  BU 546266 A 31-12-18  BU 14444 A 12-12-18  BU 14444 A 13-12-18  BU 14444 A 13-12-12-18  BU 14444 A 13-12-12-	9639384 A 12-12-1996 NOR 9639384 A 12-12-1996 NOR  AP 663934 A1 12-12  AI 701465 B2 28-01  AII 701465 B2 28-01  AII 546264 A 13-12  BIS 966254 A 13-12  CIN 1144792 A 12-20  CIN 1144792 A 12-21  DE 69223182 D1 15-11  DE 69223182 D 17-11  DE 69223182 D1 15-11  DE 69223182 D1 12-11  DE 69	oited in search report	, and	dete		member(s)		dette
9639384 A 12-12-1996 CA 2224962 AI	9639384 A 12-12-1996 CA 2224962 AI		٧	-12-199	NONE			
AP 6623 AI AI 701465 B7 AI 701465 B7 AI 5087027 T AI 5087027 T AI 508702 T AI 508702 T AI 104709 A CN 1144709 A CN 1144702 A CN 1144709 A CN 11613 B COSC244 AI CN 11613 B CN 11613	A		•	2001 61 61				
A	AT 200504 AL 623 AL 623 AL 624 AL 624 AL 624 AL 625		¢	0661-71-71	5 5			Z-1Z-1996
AT 206792 T 7 206792 T 8 8 109547 A 8 8 109547 A 8 8 109547 A 144792 A CT 1144792 A CT 1144	AT 206792 T 7 262 A A A T 206792 T 7 3 4 2 2 2 2 4 A A T 206792 T 7 4 A D T 206792 T 7 4 A D T 206792 A B B B 109547 A C T 1142492 A C T 1142492 A C T 206792 T 7 4 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2				2			2-12-1996
AT 70465 B2 AU 546592 T AU 546592 T BG 10547 A B BG 10554 A BR 960254 A BR 960254 A CN 114492 A CN 114493 B2 CN B1992 B1 CN 11613 B	AT 206702 T A 1 206702 T A 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2				¥	_	-	19-12-1997
AU 701465 B2  AU 701465 B2  BR 960554 A  CN 1144792 A  DE 69523182 D1  DE 69523182 D1  DE 69523182 T2  DE 6952465 A  HR 960244 A  LV 11613 B  NO 961664 A  NO 96666 A  CO 26469 A  NO 96666 A  CO 26469 A  NO 96666 A  NO 96666 A  CO 26469 A  NO 96666 A  CO 26469 A  NO 96666 A  CO 26469 A  NO 96666 A  NO 96666 A  CO 26469 A  NO 96666 A  CO 26469 A  CO 2646	AU 701465 B2  AU 701465 B2  BR 950554 A  CN 1142492 A  CN 1142492 A  CN 1142492 A  CN 1142492 A  CO 105554 A  CO 1142492 A  CO 105554 A				ΑT		_	5-10-2001
M. 5462696 A B B G 100547 A G G 1144792 A C G 1044792 A G G 1144792 A G G G G G G G G G G G G G G G G G G	M. 5462696 A. B. B. 106547 A. C.N. 1144792 A. C.N. 1144792 A. C.N. 1144792 A. C.N. 1144792 A. B.				T P			1000
BR 966294 A CN 114729 B CN 114729 A CN 11613 B CN 11613 A CN 11613 B C	BR 966294 A							6661-10-0
B	B G 10054 A B R 10054 A B R 10054 A B R 10054 A CN 114422 A CN 114				?			3-17-1990
RR 9662544 A CN 1144392 A CZ 9601573-A3 DE 65521182 D1 DE 65521182 D1 DE 65521182 T2 DE 711111 T1 T	RR 9662544 A CN 1144392 A CZ 960153-A3 DE 69521182 D1 DE 69521182 D1 DE 69521182 T2 DE 6952182 T2 DE 695265 A1 DE 695245 A1 DE 695247 A1 DE 6952183359 A1 DE 695218359				2		m	1-12-1996
CN 114492 A CN 114492 A CZ 9601573-18 CZ 960157-18 CZ 960157-18 CZ 960147-18 CZ 960147-18 CZ 960147-18 CZ 960147-18 CZ 96017-18 CZ 960	CN 114492 A CN 114492 A CN 114492 A CZ 9601573-63 CE 60523182 D1 CE 6052182 D1 CE 605218 D1 CE 60521 D1 CE				8		~	7-10-1998
CN 1146709 A CZ 200573-A3 DE 65923182 DI E F 0812065 A1 P F 1 DI E F 0812065 A1 DI	CN 1146709 A CZ 9604573-A3 DE 69523182 D1 DE 69523182 D1 DE 69523182 T2 DX 822665 A1 FT 94456 A HR 960244 A1 HR 960244 A1 HR 960244 A1 LV 11613 B LV 11613				3		-	2-92-1007
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DE 6992/182 12  DE 6992/182 12  F 1 082/965 A1  F 1 974/65 A  HR 960244 A1  HR 960244 A1  HR 960244 A1  1919/28 B2  KR 1119/38 A1  KR 1119/32 A1  KR 1119/32 A1  KR 119/32 A1	DE 6992182 12  DE 6992182 12  F 1 082665 A1 F 1				5			2-11-5
DK 812965 13	PA 823965 73				3			7-02-2002
FF 0824665 A1 FF1 9742665 A1 HR 9742665 A1 HR 956244 A1 HU 966244 A1 HU 9661475 A2 JP 3314928 B2 KR 131992 B1 LV 11613 B HN 96965 A KR 264466 A KR 264464 A1 KR 91848 A2 KR 26446 A1 KR 91848 A2 KR 26446 A1 KR 91848 A2 KR 91848	FF 0825965 A1 FT 974456 A1 FT 974456 A1 HR 956244 A1 HV 960244 A1 HV 960244 A1 HV 960244 A1 HV 960244 A1 HV 96024 A1 HV 96045 A HV 97456 A1 HV 96045 A HV 97456 A1				ž			9-11-2001
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HR 960244 A1 HD 19601475 A2 JP 191928 B2 KR 1191928 B1 LV 11613 B LV 11613 B NO 96066 A NO 96066 A CA 24442 C1 SG 4494 A SK 65996 A SK 65996 A CA 24447 A1 SK 65996 A3 TR 911948 A2 US 61948 A2 US 6604522 A US 6604522 A US 6604522 A US 6604533 A US 6604533 A US 6604533 B1 US 6604533 B1 US 660218338 B1 US 660218338 B1	HR 960244 A1 HD 19601475 A2 JP 131902 B1 LV 11613 B LV 11613 B LV 11613 B NO 961664 A NO 96066 A NO 96066 A NO 19606 A NO 96066 A NO 96164 A1 ST 69917 A ST 619739 A CA 234247 A1 LO 1968 A2 US CO 113111 A US 2602183389 A1 US 2602183389 A1 US 2602183389 A1 US 2602183389 A1 US 2602183389 A1				i			7-01-1000
HIN 95004757 AZ HIN 95014757 AZ JP 10511607 T JP 10511607 T JP 10511607 T HIN 11613 A HIN 950405	HO 9001475 A2  JP 10511687 T  JP 10511687 T  JP 10511687 T  JP 10511687 T  LV 11613 A  LV				: 5			10 1000
HU 9661455 A2  JP 1314938 B2  KR 1314938 B2  KR 1314938 B1  LV 11613 B  NO 999455 A 1  RV 2144424 C1  SG 44947 A1  SK 65956 A3  TR 961848 A2  US 6619329 A 6  LO 66184 A2  US 6619329 A 6  US 66295 A3  TR 961848 A2  US 662183338 A  US 662183338 A  US 662183388 A3	1088824 A 84-84-2001 B 108513687 A 1019511687 A 101951167 A 1019511687 A 1019511687 A 1019511687 A 1019511687				¥			1-12-1997
JP 19511687 T JP 19511687 T KR 191992 BL KR 191613 B KR 214345 CL KR 214345 CL KR 214456 AL KR 214345 CL KR 214345 CL KR 619199 AL KR 619396 AL KR 619396 AL KR 61939 A	JP 19511687 T JP 19511687 T KR 191992 B1 KR 191992 B1 KR 191992 B1 KR 191992 B2 KR 191992 B1 KN 951664 A KN 95164 A KN 951131181				⊋			8-69-1998
191922 B1	191922 81				J.P			8-11-1998
KR 191992 BL KR 1613 A 11613 A	C				9			
LV 11613 R LV 11613 B LV 11614 C LV 11613 B LV 11616 A LV 11613 A	1088824 A 64-64-2661 BR 1088824 A 64-84-2661 BR 1088824 A 64-84-8641 BR 1088824 A 64-84-84-84-84-84-84-84-84-84-84-84-84-84							2092-00-6
100 1151 A 11513 A 11513 A 11513 A 11513 B 10 11513 B 1	LV 11613 A LV 11613 B RV 0961664 A RV 286469 A RV 2864131181 A RV 2864133183 A RV 286413338 A RV 286469 A RV 2				ž :			5-00-T
1V 11613 B NO 961664 A NO 969405 A NZ 286469 A NZ 286469 A PL 314561 A1 SG 44947 A1 SG 44947 A1 SG 519905 A3 TR 951948 A2 US 5199329 A CA 23474 A1 CA 23474 A1 CA 23474 A1 CA 23471 A1 CA 23471 A1 US 620213339 A US 620213339 A US 620213339 A US 620213318 A US 620213339 B1	1V 1163.18 ND 91664 A ND 951664 A ND 956465 A NZ 266468 A NZ 26646 A NZ 266133181 A NZ 2661133181 A NZ 266318335 A1 NZ 266318335 A1				>	_	2	0-12-1996
NO 961664 A NO 961664 A NO 961664 A NO 961664 A NO 284469 A NO 284469 A NO 2143456 A1 NU 2143456 A1 SS 64947 A1 SS 64947 A1 SS 64947 A1 SS 6197399 A CA 2342471 A1 SS 6197399 A1 CA 2342471 A1 CA 234247	NO 961664 A NO 961664 A NO 261664 A NZ 26466 A NZ 26646 A NZ 26647 A NZ 266617 A NZ 266617 A NZ 2661131181 A NZ 266218335 A1 NZ 2662133151 A				2		~	0-04-1997
NO 999405 A NZ 286469 A NZ 286469 A PL 314561 A1 RD 214424 C1 SG 44947 A1 SG 44947 A1 SG 51 966917 A SK 6995 A3 TR 961948 A2 US 6199329 A CA 234247 A1 CA 234247 A1 D88824 A 64-64-2061 BR 6694522 A US 262183181 A US 2692183181 A US 2692183369 B1	NO 999405 A NZ 286408 A PL 286408 A PL 214561 AI 141561 AI 151561 AI 15161 AI 151561 AI 151561 AI 151561 AI 151561 AI 151561 AI 151561 A				2		ĕ	9-12-1996
N. 286460 A PL 314561 A1 RU 2143424 C1 S1 2143424 C1 S1 43437 A1 S1 6660177 A SK 65956 A3 TR 96188 A2 US 6197329 A CA 2342471 A1 CA 2342471 A1 US 6193369 A1 US 6201131181 A US 6395601 B1	N7 286469 A PL 314561 A1 RU 214424 C1 SS 44497 A1 SS 668177 A SK 66996 A3 TR 961817 A US 2342471 A1 CA 234247 A1 US 2996 A3 US 2996 A3 US 2991131181 A US 296218335 A1 US 2962183183 A1 US 2962183181 A				2		5.5	8-01-1000
PH 250400 A 11556 A 11 11556 A 115	PT 214561 A1 114561 A1 114561 A1 114561 A1 114561 A1 114561 A1 114561 A1 11561 A1 A1 11561 A1				2 2		íč	0001 00 9
1088824 A 84-64-2001 B	1088824 A 64-64-2001 BR 0894582 A 1088824 A 64-64-2001 BR 089634 BR 0894582 A 1088824				7 .		7	966T-60-6
SG 44947 C1 SG 44947 A1 SS 569177 A1 SK 669177 A1 SK 66917 A SK 66917 A SK 66917 A SK 66917 A SK 66917 A SK 66917 A1 SK 66917	SG 44947 K1 SG 44947 A1 SI 9669177 A SK 95996 A3 TR 961917 A TR 961918 A2 US 6197329 A CA 2342471 A1 1088624 A 2 JP 2091131181 A US 2092133359 A1 US 2092133183 A1 US 2092133183 A1				<del>ل</del> ا	314561		9-12-1996
SG 44947 A1 SI 64947 A1 SI 65996 A3 SK 65996 A3 SI 65996 A3 SI 65996 A3 SI 65996 A3 SI 6447 A1 SI 64996 A3 SI 64997 A1 SI 64996 A3 SI 64997 A1 SI 6499	SG 44947 A1 SI 668177 A SK 66996 A3 TR 95188 A2 US 2342471 A1 CA 234247 A1 1088824 A 64-64-2691 BR 6894582 A US 2062183359 A1 US 206218335 A1 US 206218335 A1				2	143424		7-12-1999
S1 966017 A SK 6995 A3 TR 951946 A2 US 61895 29 A TR 951948 A2 US 61895 A3 TR 951946 A2 US 234241 A1 TR 951946 A2 US 234241 A1 US 234241 A1 US 2343151 A1 US 2343151 A1 US 2343151 A1 US 2343151 A1	S1 966917 A SK 65995 A3 TR 951848 A2 US 6197329 A US 6197329 A US 6197329 A CA 2342471 A1 1088824 A 84-84-2691 BR 686552 A US 2692183181 A US 2692183183 A1 US 639561 B1				Š	-	ĭ	9-12-1997
SK 68996 A3 TR 961848 A2 US 6187329 A CA 2342471 A1 CA 2342471 A1 CA 2342471 A1 CA 2342471 A1 DE 686824 A2 DE 686824 A2 US 2662183369 A1 US 2662183369 B1	SK 69996 A3 TR 961948 A2 US 6107329 A CA 2342471 A1 1088824 A 64-64-2691 BR 6894582 A US 2062183359 A1 US 2062183359 A1 US 2062183359 A1				7	500177	7	A-02-1997
TR 961998 AS TR 961948 AS CA 513421 AI 1088824 A 64-84-2661 BR 6894582 A UP 2692113181 A US 2692183369 AI US 2692183369 AI US 2692183369 AI	TR 961894 A2 US 6187329 A2 US 6187329 A CA 234241 A1 1088824 A 84-84-2691 BR 6864582 A JP 2091131181 A US 2662183359 A1 US 6399601 B1				; ;	20003		1001
18 501989 AZ 21-12 18 6197329 A 22-08 CA 2342471 A1 12-12 2342471 A1 12-12 EP 186822 A 17-04 US 2062181181 A 15-05 US 2062181319 A 15-05 US 2062181369 A1 15-05 US 2062181369 A1 15-05	18 610729 4 22-18 1088824 A 64-84-2601 BR 6804562 A 17-64 19 2004582 A 17-64 19 2001131181 A 15-69 10 2002183181 A 15-69 10 2002183181 A 15-69 10 6399601 B1 04-66				ć i	_		/66T-00-0
US 6197329 A 22-08  CA 242471 A1 12-12  1088824 A 64-94-2091 BR 6994582 A 17-04  P 1086824 A2 04-04  US 2992133181 A 15-05  US 299213181 A 15-05  US 299213181 A 15-05	US 6187329 A 22-08  CA 2342471 A1 12-12  1088624 A 04-84-2601 BR 0896452 A 17-04  JP 2091131181 A 15-05  US 2062183359 A1 05-12  US 2062183359 A1 05-12  US 2062183159 A1 05-12				<u>*</u>	-	2	?
CA 2342471 A1 12-12 1088824 A 04-84-2001 BR 0894582 A 17-04 FP 1188824 A2 04-04 US 2082183181 A 15-05 US 208218359 A1 06-12 US 6399661 B1 04-06	CA 2342471 A1 12-12 1088824 A 64-64-2061 BR 6864582 A 17-04 P 1086824 A2 04-04 JP 2091131181 A 15-05 US 2062181318 A 15-05 US 639961 B1 04-06				S	6107329 A	**	ç
1088824 A 04-64-2001 BR 6804582 A 17-04-2 EP 1088824 A2 04-04-04-3 JP 2001131181 A 15-05-2 US 200218359 A1 05-12-2 US 539601 B1 04-06-2	108824 A 64-64-2661 BR 6864582 A 17-04-2 EP 168884 AZ 64-04-04-04-2 JP 2691131181 A 15-05-2 US 2692183369 A1 65-12-2 US 6399601 B1 04-06-2				5		i≌	::
1088824 A 64-04-2001 BR 9894562 A 17-04 EP 1088824 A2 04-04 JP 2001131181 A 15-05 US 2002183369 A1 65-12 US 6395601 B1 04-06	1088824 A 04-04-2001 BR 0890482 A 17-04 P 1088024 A2 04-04 JP 2001131181 A 15-05 US 2002183359 A1 05-12 US 6399601 B1 04-06							
1088024 A2 04-04 2091131181 A 15-05 2092183369 A1 05-12 6399601 B1 04-06	2091131181 A 2 04-04 2092183189 A1 65-12 6399681 B1 04-06		⋖	64-64-2661	88	0994582 A	17	ģ
2002131181 A 15-05 2002183369 A1 05-12 6399601 B1 04-06	2001131181 A 15-05 200218350 A1 06-12 6399601 B1 04-06			٠			č	ě
2002183369 A1 05-12 6399601 B1 04-06	2002183369 A1 65-12 6399661 B1 04-66						. =	ģ
6399601 B1 04-06	21-500 11 09-600 00-0000 00-000 00-000 00-000 00-000 00-000 00-000 00-000 00-000 00-0000 00-000 00-000 00-000 00-000 00-000 00-000 00-000 00-000 00-0000 00-000 00-000 00-000 00-000 00-000 00-000 00-000 00-000 00-0000 00-000 00-000 00-000 00-000 00-000 00-000 00-000 00-000 00-0000 00-000 00-000 00-000 00-000 00-000 00-000 00-000 00-000 00-0000 00-000 00-000 00-000 00-000 00-000 00-000 00-000 00-000 00-0000 00-000 00-000 00-000 00-000 00-000 00-000 00-000 00-000 00-0000 00-000 00-000 00-000 00-000 00-000 00-000 00-000 00-000 00-0000 00-000 00-000 00-000 00-000 00-000 00-000 00-000 00-000 00-0000 00-000 00-000 00-000 00-000 00-000 00-000 00-000 00-000 00-0000 00-000 00-000 00-000 00-000 00-000 00-000 00-000 00-000 00-000000						: 2	3;
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